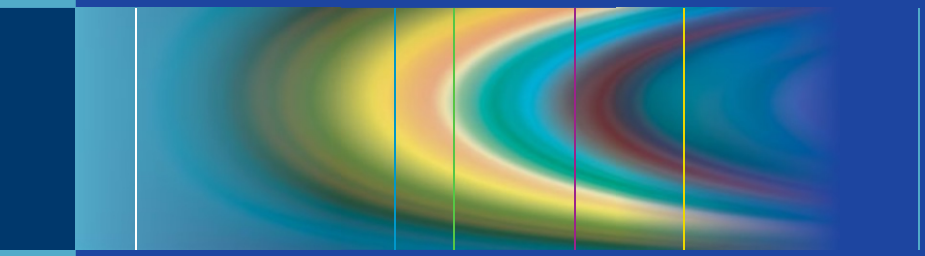
David Hui
Alexander A. Leung
Raj Padwal *Editors*



Approach to Internal Medicine

A Resource Book for Clinical Practice

Fourth Edition

Springer

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Edited by

David Hui, MD, MSc
Alexander A. Leung, MD, MPH, FRCPC, MRCP(UK), FACP
Raj Padwal, MD, MSc, FRCPC

With Assistance from

Christopher Ma, MD

Springer

Editors
David Hui, MD, MSc
The University of Texas MD Anderson Cancer Center
Houston, TX
USA

Raj Padwal, MD, MSc, FRCPC
University of Alberta
Edmonton, AB
Canada

Alexander A. Leung, MD, MPH, FRCPC, MRCP(UK), FACP
University of Calgary
Calgary, AB, Canada

Editors: David Hui, Alexander A. Leung, Raj Padwal
Assistant Editor: Christopher Ma

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To Ella, Rupert and Nancy
David Hui

To Miriam
Alexander A. Leung

To Stephanie and Sarah
Raj Padwal

To Bryan, Sarah, Michael, and May
Christopher Ma

Disclaimer

Approach to Internal Medicine is meant to be a practical field guide. Dosages of medications are provided for quick reference only. Readers should consult other resources before applying information in this manual for direct patient care. The author, editors, and publisher of *Approach to Internal Medicine* cannot be held responsible for any harm, direct or indirect, caused as a result of application of information contained within this manual.

Preface

Practice is science touched with emotion.
Confessio Medici, Stephen Paget, 1909

In this fourth edition of *Approach to Internal Medicine,* we have substantially updated the content to provide practicing clinicians and trainees with a practical, evidence-based, and concise resource for everyday clinical use, bedside teaching and examination preparation. *Approach to Internal Medicine* consists of over 250 internal medicine topics classified under 17 subspecialties.

Under each topic, the sections on differential diagnoses, investigations, and treatments are designed for the rapid retrieval of high-yield clinical information and can be particularly useful when one is all alone assessing a patient at 3 o'clock in the morning. Unique to *Approach to Internal Medicine,* we have included multiple comparison tables aimed at highlighting the distinguishing features between various clinical entities, and numerous clinical pearls and mnemonics (marked by ★). In addition to International System (SI) units, this edition also provides US customary units [in square brackets] for quick reference.

For this new edition, we are very fortunate to have recruited a new assistant editor, Dr. Christopher Ma, who brings with him a wealth of knowledge and the perspective of a chief medicine resident. *The JAMA Rationale Examination Series has now been updated with new data*. We are most grateful to our section editors and contributors for their meticulous review of each subspecialty, providing expert input on the most up-to-date information. We also would like to thank the editorial and production teams at Springer for their expert guidance and support throughout this mammoth project. Finally, we would like to thank all previous and current users of this manual for their support and feedback.

While every effort has been made to ensure the accuracy of information in this manual, the author, editors, and publisher are not responsible for omissions, errors, or any consequences that result from application of the information contained herein. Verification of the information in this manual remains the professional responsibility of the practitioner. Readers are strongly urged to consult other appropriate clinical resources prior to applying information in this manual for direct patient care. This is particularly important since patterns of practice and clinical evidence evolve constantly. We welcome any constructive feedback to help make this manual a more accurate, practical, comprehensive, and user-friendly resource.

David Hui, MD, MSc
The University of Texas MD Anderson Cancer Center
Houston, TX, USA

Alexander A. Leung, MD, MPH, FRCPC, MRCP(UK), FACP
University of Calgary,
Calgary, AB, Canada

Raj Padwal, MD, MSc, FRCPC
University of Alberta
Edmonton, AB, Canada

Christopher Ma, MD
Department of Medicine, University of Alberta,
Edmonton, AB, Canada

Section Editors

PULMONARY MEDICINE
Ashley-Mae Gillson, HBSc, MD, FRCPC
Division of Pulmonary Medicine
Department of Medicine
University of Alberta
Edmonton, AB, Canada

CARDIOLOGY
Bryan Jonathan Har, MD, MPH, FRCPC
Clinical Assistant Professor
Department of Cardiac Sciences
University of Calgary
Calgary, AB, Canada

NEPHROLOGY
Alan W. McMahon, MD, FRCPC
Division of Nephrology and Transplant Immunology
Department of Medicine
University of Alberta
Edmonton, AB, Canada

CRITICAL CARE
Wendy Sligl, MD, MSc, FRCPC
Divisions of Critical Care Medicine
and Infectious Diseases
Department of Medicine
University of Alberta
Edmonton, AB, Canada

GASTROENTEROLOGY
Angeli Chopra, MD, FRCPC, ABIM
Division of Gastroenterology
Department of Medicine
University of Alberta
Edmonton, AB, Canada

HEMATOLOGY
Michael H. Kroll, MD, FACP
Department of Benign Hematology
The University of Texas MD Anderson
Cancer Center
Houston, TX, USA

ONCOLOGY
Ahmed Eid, MD, MEd
Department of General Oncology
The University of Texas MD
Anderson Cancer Center
Houston, TX, USA

David Ramirez, MD
Department of General Oncology
The University of Texas MD
Anderson Cancer Center
Houston, TX, USA

Caren L. Hughes, PharmD, BCOP
Division of Pharmacy
The University of Texas MD
Anderson Cancer Center
Houston, TX, USA

INFECTIOUS DISEASES
Stephanie W. Smith, MD, MSc, FRCPC
Division of Infectious Diseases
Department of Medicine
University of Alberta
Edmonton, AB, Canada

RHEUMATOLOGY
Steven J. Katz, MD, FRCPC
Division of Rheumatology
Department of Medicine
University of Alberta
Edmonton, AB, Canada

NEUROLOGY
Michael M.C. Yeung, MD, FRCPC
Department of Clinical Neurosciences
Cumming School of Medicine
University of Calgary
Calgary, AB, Canada

Ronak K. Kapadia, MD, BSc
Department of Clinical Neurosciences
Cumming School of Medicine
University of Calgary
Calgary, AB, Canada

ENDOCRINOLOGY

Sonia Butalia, BSc, MD, FRCPC, MSc
Division of Endocrinology
and Metabolism
Department of Medicine
University of Calgary
Calgary, AB, Canada

DERMATOLOGY

Susan Y. Chon, MD, FAAD
Division of Internal Medicine
Department of Dermatology
The University of Texas MD
Anderson Cancer Center
Houston, TX, USA

GERIATRICS

Diana Rucker, MSc, MD, FRCPC
Division of Geriatrics
Department of Medicine
University of Alberta
Edmonton, AB, Canada

PALLIATIVE CARE

David Hui, MD, MSc
Department of Palliative Care
and Rehabilitation Medicine
Department of General Oncology
Division of Cancer Medicine
The University of Texas MD
Anderson Cancer Center
Houston, TX, USA

NUTRITION

Raj Padwal, MD, MSc, FRCPC
Division of General Internal Medicine
Department of Medicine
University of Alberta
Edmonton, AB, Canada

Kari McKnight, RD
WholeSUM Nutrition Consulting Inc.
Edmonton, AB, Canada

OBSTETRICAL MEDICINE

Eliana Castillo, MD, MHSc, FRCPC
Division of General Internal Medicine
Department of Medicine
Cumming School of Medicine
University of Calgary
Calgary, AB, Canada

Tammy Shaw, MD, CCFP, FRCPC
Division of General Internal Medicine
Department of Medicine
St. Joseph's Health Centre
University of Toronto
Toronto, ON, Canada

GENERAL INTERNAL MEDICINE

Peter Hamilton, MBBCh, FRCPC
Division of General Internal Medicine
Department of Medicine
University of Alberta
Edmonton, AB, Canada

Christopher Ma, MD
Department of Medicine
University of Alberta
Edmonton, AB, Canada

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1
PULMONARY MEDICINE

Ashley-Mae Gillson

Asthma Exacerbation

DIFFERENTIAL DIAGNOSIS OF WHEEZING

EXTRATHORACIC AIRWAY OBSTRUCTION

- **OROPHARYNX**—enlarged tonsils, retropharyngeal abscess, obesity, post-nasal drip
- **LARYNX**—laryngeal edema, laryngostenosis, laryngocele, epiglottitis, anaphylaxis, severe laryngopharyngeal reflux, laryngospasm
- **VOCAL CORDS**—vocal cord dysfunction, paralysis, hematoma, tumor, cricoarytenoid arthritis

INTRATHORACIC AIRWAY OBSTRUCTION

- **TRACHEAL OBSTRUCTION**—tracheal stenosis, tracheomalacia, tracheobronchitis (herpetic, fungal), malignancy, benign tumor, aspiration, foreign body
- **TRACHEAL COMPRESSION**—goiter, right-sided aortic arch
- **LOWER AIRWAY OBSTRUCTION**—asthma, COPD, bronchiolitis, bronchiectasis, carcinoid tumor, aspiration, malignancy
- **PARENCHYMA**—pulmonary edema
- **VASCULAR**—pulmonary embolism

PATHOPHYSIOLOGY

EXACERBATORS OF ASTHMA

- **INFECTIONS**—viral, bacterial, fungal
- **OUTDOORS**—respirable particulates, ozone, sulfur dioxide, cold air, humidity, smoke
- **INDOORS**—smoke, dust mites, air conditioners, humidity, perfumes, scents, mold, animal dander
- **NON-ADHERENCE**

CLINICAL FEATURES

HISTORY—history of asthma and any life-threatening exacerbations, number of ER visits/hospital admissions in the last 6 months (or ever), any ICU admissions, previous prednisone use, triggers for attacks, usual peak expiratory flow rate, change in peak flow rates, wheezing, cough, dyspnea, decreased function, exercise limitation, nocturnal symptoms,

CLINICAL FEATURES (CONT'D)

absenteeism from work/school, postnasal drip, recurrent sinusitis, GERD, past medical history, medication history, psychosocial issues, occupational and work environment, home environment (pets, heating source, filter changes)

PHYSICAL—HR ↑, RR ↑, pulsus paradoxus, O_2 requirement, moderate-severe dyspnea, barrel chest, cyanosis, hyperresonance, decreased breath sounds, wheezing, forced expiratory time

TYPES OF WHEEZING—inspiratory wheeze and expiratory wheeze are classically associated with extrathoracic and intrathoracic airway obstruction, respectively. However, they are neither sensitive nor specific and cannot help to narrow differential diagnosis

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, troponin/CK
- **MICROBIOLOGY**—sputum Gram stain/AFB/C&S, nasopharyngeal swab for viral studies
- **IMAGING**—CXR

SPECIAL

- **ABG**—if acute respiratory distress
- **PEAK FLOW METER**—need to compare bedside reading to patient's baseline
- **SPIROMETRY/PFT** (non-acute setting)—↑ FEV1 >12% and an absolute ↑ by 200 mL post-bronchodilator suggests asthma
- **METHACHOLINE CHALLENGE** (non-acute setting)—if diagnosis of asthma not confirmed by spirometry alone. A decrease of FEV1 >20% after methacholine challenge suggests asthma. Sens 95%
- **SPUTUM EOSINOPHIL COUNTS** (non-acute setting)—performed in specialized centres for monitoring of asthma control in patients with moderate to severe asthma

Can Resp J 2012 19:2

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ACUTE MANAGEMENT

ABC—**O_2** to keep sat >92%, IV

BRONCHODILATORS—***salbutamol*** 100 μg MDI 2 puffs q6h ATC + q1h PRN and ***ipratropium*** 20 μg MDI 2 puffs q6h ATC (frequency stated is only a guide, may increase or decrease on a case by case basis)

STEROID—***prednisone*** 0.5–1 mg/kg PO daily × 7–14 days (may be shorter depending on response) or ***methylprednisolone*** 0.4–0.8 mg/kg IV daily (until conversion to prednisone)

OTHERS—if refractory case and life-threatening, consider IV epinephrine, IV salbutamol, theophylline, inhaled anesthetics, $MgSO_4$

MECHANICAL VENTILATION—**BiPAP**, **intubation**

LONG-TERM MANAGEMENT

EDUCATION—**smoking cessation** (see p. 480). **Asthma action plan. Puffer technique** education and review

ENVIRONMENTAL CONTROL—**avoidance** of outdoor/indoor allergens, irritants, and infections; home environment cleanliness (e.g. steam cleaning)

VACCINATIONS—influenza vaccine annually and pneumococcal vaccine every 5 years

FIRST LINE—**SABA** (*salbutamol* 100 μg MDI 2 puffs PRN). Proceed to second line if using more than 2×/week or 1×/day for exercise-induced symptoms, symptoms >2×/week, any nocturnal symptoms, activity limitation or PEF <80%

SECOND LINE—low-dose **ICS** plus short-acting β2-agonist PRN

THIRD LINE—moderate-dose **ICS**, combined **ICS** plus **LABA** (note that long-acting β2-agonist should never be used alone in asthma), or **leukotriene receptor antagonist** (most effective in asthma complicated with sinus disease and exercise-induced asthma). May also consider using single inhaler budesonide/formoterol combination therapy as both a controller and an acute reliever

FOURTH LINE—**anti-IgE therapy** (omalizumab) for refractory allergic asthma, administered subcutaneously q2–4 weeks, dosed by IgE level and body weight, for add-on therapy or inadequately controlled moderate-to-severe allergic asthma despite use of high doses of inhaled corticosteroid therapy

NEJM 2009 360:10
Can Resp J 2012 19:2

TREATMENT ISSUES

ASTHMA CONTROL CRITERIA

Characteristic	Frequency or value
Daytime symptoms	<4 days/week
Night-time symptoms	<1 night/week
Physical activity	Normal
Exacerbations	Mild, infrequent
Absence from work or school due to asthma	None
Need for a SABA	<4 doses/week
FEV1 or PEF	≥90% personal best
PEF diurnal variation[a]	<10–15%
Sputum eosinophils	<2–3%

[a]Diurnal variation is calculated as the difference between the highest and lowest PEF divided by the highest PEF multiplied by 100 for morning and night (determined over a 2 week period)

COMMON INHALED MEDICATIONS

- **SHORT-ACTING β-AGONISTS (SABA)**—*salbutamol* MDI 100 μg 1–2 puffs PRN or 2.5 mg NEB PRN, *fenoterol* MDI 100 μg 1–2 puffs PRN, *terbutaline* 500 μg INH PRN
- **SHORT-ACTING ANTICHOLINERGICS**—*ipratropium* MDI 20 μg 2 puffs QID or 500 μg NEB QID
- **LONG-ACTING β-AGONISTS (LABA)**—*formoterol* 6–24 μg INH BID, *salmeterol* diskus 50 μg i puff BID
- **LONG-ACTING ANTICHOLINERGICS**—*tiotropium* 18 μg INH daily
- **INHALED CORTICOSTEROIDS**—*beclomethasone* 125–250 μg INH BID, *budesonide* turbuhaler 200–400 μg INH BID or 0.5–1 mg NEB BID, *fluticasone* 125–250 μg INH BID, *ciclesonide* MDI 100–400 μg INH daily (only indicated for asthma at this time, not COPD), *mometasone twisthaler* 100–400 μg INH BID

Related Topics
Chronic Obstructive Pulmonary Disease (p. 4)
Pulmonary Function Tests (p. 25)

TREATMENT ISSUES (CONT'D)

ADMISSION CRITERIA

	FEV1 (L)	PEF (L/min)	PaO_2	Action
Very severe	–	–	<90% with O_2	Admit
Severe	<1.6 (<40%)	<200 (<40%)	<90%	Admit
Moderate	1.6–2.1	200–300	>90%	Admit?
Mild	>2.1 (>60%)	>300 (>60%)	>90%	Send home

DISCHARGE CRITERIA—consider discharging patient if peak flow >70% of usual (or predicted) value for at least 1 h after bronchodilator

OXYGEN DELIVERY DEVICES

Device	Flow rates	Delivered O_2
Nasal cannula	1 L/min	21–24%
	2 L/min	25–28%
	3 L/min	29–32%
	4 L/min	33–36%
	5 L/min	37–40%
	6 L/min	41–44%
Simple oxygen face mask	6–10 L/min	35–60%
Face mask with oxygen reservoir (non-rebreather mask)	6 L/min	60%
	7 L/min	70%
	8 L/min	80%
	9 L/min	90%
	10–15 L/min	95 + %
Venturi mask	4–8 L/min	24–40%
	10–12 L/min	41–50%

NOTE: delivered O_2 (FiO_2) is approximate. Oxygen delivery can approach 100% with intubation and mechanical ventilation

SPECIFIC ENTITIES

EXERCISE-INDUCED ASTHMA

- **PATHOPHYSIOLOGY**—mild asthma with symptoms only during exercise due to bronchoconstriction as a result of cooling of airways associated with heat and water loss
- **DIAGNOSIS**—spirometry. Exercise or methacholine challenge may help in diagnosis
- **TREATMENTS**—prophylaxis with *salbutamol* 2 puffs MDI, given 5–10 min before exercise. Consider leukotriene antagonists or inhaled glucocorticoids if frequent use of prophylaxis

TRIAD ASTHMA (Samter's syndrome)—triad of asthma, aspirin/NSAIDs sensitivity, and nasal polyps. Cyclooxygenase inhibition → ↓ prostaglandin E_2 → ↑ leukotriene synthesis → asthma symptoms. Management include ASA/NSAIDs avoidance and leukotriene antagonists (montelukast)

SPECIFIC ENTITIES (CONT'D)

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA)

- **PATHOPHYSIOLOGY**—associated with asthma and cystic fibrosis. Due to colonization of the airways by *Aspergillus fumigatus*, leading to an intense, immediate hypersensitivity-type reaction in the airways
- **CLINICAL FEATURES**—history of asthma, recurrent episodes of fever, dyspnea, and productive cough (brownish sputum). Peripheral eosinophilia. CXR findings of patchy infiltrates and central bronchiectasis, CT chest findings of central bronchiectasis, "finger-in-glove" appearance (i.e. mucous-filled dilated bronchi)
- **DIAGNOSIS**—above clinical features plus *Aspergillus* extract skin test, serum IgE level, sputum for *Aspergillus* and/or serologic tests (IgE and IgG against *Aspergillus*)
- **TREATMENTS**—systemic glucocorticoids, itraconazole

COPD Exacerbation NEJM 2004 250:26

DIFFERENTIAL DIAGNOSIS OF ACUTE DYSPNEA

RESPIRATORY

- **AIRWAY**—COPD exacerbation, asthma exacerbation, acute bronchitis, infectious exacerbation of bronchiectasis, foreign body obstruction
- **PARENCHYMA**—pneumonia, cryptogenic organizing pneumonia (COP), ARDS, acute exacerbation of interstitial lung disease
- **VASCULAR**—pulmonary embolism, pulmonary hypertension
- **PLEURAL**—pneumothorax, pleural effusion

CARDIAC

- **MYOCARDIAL**—HF exacerbation, myocardial infarction
- **VALVULAR**—aortic stenosis, acute aortic regurgitation, mitral stenosis, endocarditis
- **PERICARDIAL**—pericardial effusion, tamponade

SYSTEMIC—sepsis, metabolic acidosis, anemia

OTHERS—neuromuscular, psychogenic, anxiety

PATHOPHYSIOLOGY

PRECIPITANTS OF COPD EXACERBATION—infections, lifestyle/environmental (10% [cigarette smoke, dust, pollutants, cold air]), non-adherence, pulmonary embolism, pulmonary edema, pneumothorax, progression of COPD

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THE CLINICAL EXAMINATION PREDICT AIRFLOW LIMITATION?

	LR+	LR–
History		
Smoking >40 pack-years	*12*	*0.63*
Smoking ever	1.8	0.16
Sputum >1/4 cup	4	0.84
Chronic bronchitis Sx	3	0.78
Wheezing	3.8	0.66
Any exertional dyspnea	2.2	0.83
Coughing	1.8	0.69
Any dyspnea	1.2	0.55
Physical		
Barrel chest	10	0.90
Decreased cardiac dullness	10	0.88
Match test	7.1	0.43
Rhonchi	5.9	0.95
Hyperresonance	4.8	0.73
FEV1 >9 s	4.8	–
FEV1 6–9 s	2.7	–
FEV1 <6 s	0.45	–
Subxyphoid cardiac apical impulse	4.6	0.94
Wheezing	*4.4*	*0.88*
Maximum laryngeal height ≤4 cm	*4.2*	*0.70*
Pulsus paradoxus (>15 mmHg)	3.7	0.62
Decreased breath sounds	*2.6*	*0.66*
Accessory muscle use	–	0.70
Clinical Judgement		
Overall Clinical Prediction of Moderate-Severe Disease	*5.6*	–
Overall Clinical Prediction of Mild Disease	*2.3*	–

APPROACH—"no single item or combination of items from the clinical examination rules out airflow limitation. The best findings associated with increased likelihood of airflow limitation are objective wheezing, FEV1 >9 s, positive match test, barrel chest, hyperresonance and subxyphoid cardiac impulse. Three findings predict the likelihood of airflow limitation in men: years of cigarette smoking, subjective wheezing and either objective wheezing or peak expiratory flow rate"

JAMA 1995 273:4

UPDATE—multivariate 'Rule In' Obstructive Disease Model (history of obstructive airways disease, smoking >40 pack-years, age ≥45, and laryngeal height ≤4 cm) has posterior odds of disease of 220. Multivariate 'Rule Out' Obstructive Disease Model (smoking <30 years, no wheezing symptoms, and no auscultated wheezing) has posterior odds of disease of 0.02.

The Rational Clinical Examination. McGraw-Hill, 2009

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, troponin/CK, Ca, Mg, PO_4
- **MICROBIOLOGY**—sputum Gram stain/AFB/C&S/fungal, nasopharyngeal swab for viral studies
- **IMAGING**—CXR
- **ECG**—left atrial enlargement, atrial fibrillation, sinus tachycardia
- **SPIROMETRY/PFT**—FEV1/FVC <0.7, may be partially reversible. Severity based on FEV1
- **ABG**—if acute respiratory distress

SPECIAL

- **BNP**—if suspect HF
- **D-DIMER, CT CHEST**—if suspect PE
- **ECHOCARDIOGRAM**

PROGNOSTIC ISSUES

PROGNOSIS OF PATIENTS WITH ACUTE EXACERBATION OF COPD—in-hospital mortality 5–10%

GOLD CLASSIFICATION 2007—all have FEV1/FVC <0.7

- **STAGE I (MILD)**—FEV1 ≥ 80% predicted
- **STAGE II (MODERATE)**—FEV1 50–79% predicted
- **STAGE III (SEVERE)**—FEV1 30–49% predicted
- **STAGE IV (VERY SEVERE)**—FEV1 < 30% predicted, or <50% predicted + cor pulmonale

BODE INDEX

- **BMI**—0 points = >21, 1 point = ≤21
- **OBSTRUCTION** (post-bronchodilator FEV1)—0 points = ≥65% predicted, 1 point = 50–64%, 2 points = 36–49%, 3 points = ≤35%
- **DISTANCE WALKED IN 6 MIN**—0 points = ≥350 m, 1 point = 250–349 m, 2 points = 150–249 m, 3 points = ≤149 m
- **EXERCISE MMRC DYSPNEA SCALE**—0 points = 0–1, 1 point = 2, 2 points = 3, 3 points = 4
- **SCORING**—total BODE score calculated as sum of all points. Relative risk for death (any cause) is increased by 34% per one-point increase in BODE score. Relative risk for death (from respiratory failure, pneumonia, or pulmonary embolism) is increased by 62% per one-point increase in BODE score

NEJM 2004 350:10

ACUTE MANAGEMENT

ABC—**O_2** to keep sat >90%, or 88–92% if CO_2 retainer, IV

BRONCHODILATORS—***salbutamol*** 100 µg MDI 2 puffs q4h ATC + q1h PRN and ***ipratropium*** 20 µg MDI 2 puffs q4h ATC

STEROIDS—***prednisone*** 40–60 mg PO daily × 5–14 days (tapering dose not always necessary) or ***methylprednisolone*** 60–125 mg IV q6-12 h (inpatient)

ANTIBIOTICS—give if any two of the following criteria are met: ↑ sputum purulence, ↑ dyspnea or ↑ sputum volume. Other considerations include the need for non-invasive mechanical ventilation and "at risk" for poor outcome (substantial comorbidities, severe COPD, frequent exacerbations >3/year, recent antibiotics within 3 months); choices depend on clinical circumstance (*levofloxacin* 500 mg PO daily × 7–10 days [or 750 mg PO daily × 5 days if no renal disease], *doxycycline* 100 mg PO BID × 7–10 days, *amoxicillin* 500 mg PO BID × 7 days, *cefuroxime* 250–500 mg PO BID × 10 days, or *azithromycin* 500 mg PO × 1 day then 250 mg PO daily × 4 days)

MECHANICAL VENTILATION—**BiPAP**, **intubation**

OTHERS—DVT prophylaxis (*unfractionated heparin* 5000 U SC q8-12 h, *enoxaparin* 40 mg SC q24h, *dalteparin* 5000 U SC q24h), physiotherapy

NEJM 2002 346:13

LONG-TERM MANAGEMENT

EDUCATION—**smoking cessation** (see p. 480). Disease-specific self-management program. **Puffer technique** education and review

VACCINATIONS—influenza vaccine annually and pneumococcal vaccine booster every 5 years

REHABILITATION—**education** and **exercise training** (increases quality of life and exercise tolerance); **pulmonary rehabilitation** associated with ↓ risk of recurrent exacerbation in patients with moderate to very severe COPD and recent AECOPD (<4 weeks)

FIRST LINE—**SABA** or short-acting anticholinergic on an as-needed basis

SECOND LINE—**LABA** or **long-acting anticholinergic** (*tiotropium* 1 puff [18 µg/puff] INH daily) plus SABA PRN. Consider early initiation of long-acting agents if requiring regular PRN short-acting agents as long-acting agents are superior

LONG-TERM MANAGEMENT (CONT'D)

THIRD LINE—**LABA** plus **long-acting anticholinergic**, with SABA PRN

FOURTH LINE—**long-acting anticholinergic** plus **LABA/ICS** (e.g. Advair, Symbicort). No role for ICS monotherapy. Consider **phosphodiesterase-4 inhibitor** (*roflumilast* 500 µg PO daily) as adjuvant maintenance therapy in moderate to severe COPD with ≥1 exacerbation in previous year. Consider **mucolytic agents** (*N-acetylcysteine* 10–20% solution NEB TID-QID, *carbocysteine* 375–750 mg PO TID) if ≥2 exacerbations in previous 2 years. Chronic antibiotic therapy generally not recommended

FIFTH LINE—fourth line plus ***theophylline*** 400 mg PO daily × 3 days, then 400–600 mg PO daily, therapeutic level 10–20 µg/mL

SIXTH LINE—fifth line plus **home O_2**

SEVENTH LINE—**lung volume reduction surgery** (may be beneficial if upper lobe involvement and poor functional capacity) or **lung transplant**

Canadian Thoracic Society COPD Guidelines 2007

American College of Chest Physicians (CHEST) and Canadian Thoracic Society (CTS) Joint Guidelines 2014

TREATMENT ISSUES

FACTORS FOR IMPENDING INTUBATION—cardiac or respiratory failure, hemodynamic instability, markedly elevated respiratory rate (>35/min), fatigue and labored respiration, use of accessory muscles, worsening hypercapnia, acidosis (especially lactic), stridor (impending upper airway obstruction), agonal breathing (impending respiratory arrest)

LIFE-PROLONGING MEASURES FOR COPD—smoking cessation, supplemental O_2, lung transplant

INDICATIONS FOR SUPPLEMENTAL HOME O_2—ABG done at room air. PaO_2 <55 mmHg alone or PaO_2 <60 mmHg in the presence of bilateral ankle edema, cor pulmonale, or hematocrit >56%

SPECIFIC ENTITIES

α1-ANTITRYPSIN DEFICIENCY

- **PATHOPHYSIOLOGY**—production of an abnormal protease inhibitor (homozygous ZZ) with impaired transport out of the liver. Serum level is only 10–15% of normal → increased protease activity leads to emphysema and cirrhosis (10%)
- **DIAGNOSIS**—α1-antitrypsin levels; targeted testing should be considered in patients with COPD diagnosed before 65 years of age or with a smoking history of <20 pack years

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—similar to COPD, α1-antitrypsin replacement

BRONCHIOLITIS OBLITERANS

- **PATHOPHYSIOLOGY**—severe inflammation of bronchioles → airflow obstruction. Very different from bronchiolitis obliterans organizing pneumonia (BOOP)/cryptogenic organizing pneumonia (COP), a parenchymal lung disorder
- **CAUSES**—infection (viral, mycoplasma), inflammatory (ulcerative colitis, rheumatoid arthritis), transplant (bone marrow, lung), toxic fumes, idiopathic
- **TREATMENTS**—bronchiolitis obliterans (with an organizing intraluminal exudate and proliferative granulation tissue polyp) is usually steroid responsive. Constrictive bronchiolitis (late, fibrotic, concentric) is not responsive to glucocorticoids

BRONCHIECTASIS

- **PATHOPHYSIOLOGY**—airway obstruction, destruction, altered immunity → ↑ cellular and mediator inflammatory response → ↑ elastase, sputum production → recurrent infections → vicious cycle → permanent dilatation of bronchi. Major types of bronchiectasis include
  - **CYLINDRICAL OR TUBULAR BRONCHIECTASIS**—dilated airways alone, sometimes represents residual effect of pneumonia and may resolve
  - **VARICOSE BRONCHIECTASIS**—focal constrictive areas along the dilated airways
  - **SACCULAR OR CYSTIC BRONCHIECTASIS**—most severe form. Progressive dilatation of the airways, resulting in large cysts or saccules
- **CAUSES**
  - **FOCAL**—broncholith, post-infectious, tumor, extrinsic lymph node compression, post-lobar resection, recurrent aspiration
  - **DIFFUSE**
    - **POST-INFECTIOUS**—bacterial (*Pseudomonas, Haemophilus*), mycobacterium, fungal, viral (adenovirus, measles, influenza, HIV)
    - **IMMUNODEFICIENCY**—cancer, chemotherapy, hypogammaglobulinemia, immunosuppression, sequelae of toxic inhalation or aspiration of foreign body
    - **INTERSTITIAL LUNG DISEASE**—traction bronchiectasis
    - **INFLAMMATORY**—RA, SLE, Sjogren's syndrome, relapsing polychondritis, IBD
    - **INHERITED**—α1-antitrypsin deficiency, cystic fibrosis, primary ciliary dyskinesia

SPECIFIC ENTITIES (CONT'D)

(Kartagener's syndrome, Young's syndrome), tracheobronchomegaly (Mounier–Kuhn syndrome), cartilage deficiency (Williams–Campbell syndrome), Marfan's syndrome

- **DIAGNOSIS**—high-resolution CT chest (signet ring sign), PFT (obstruction ± reversibility)
- **TREATMENTS**—exercises, chest physiotherapy, and bronchodilators similar to COPD; however, if reversible, inhaled corticosteroids should be given early. Ensure adequate systemic hydration. Effective treatment of exacerbations

NEJM 2002 346:18

SPECIFIC ENTITIES (CONT'D)

Related Topics
Cryptogenic Organizing Pneumonia (p. 18)
Pulmonary Function Tests (p. 25)
Smoking (p. 480)

Pneumonia

NEJM 2002 345:25; NEJM 2001 344:9

TYPES OF PNEUMONIA

COMMUNITY-ACQUIRED PNEUMONIA

- **BACTERIAL**—*Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus*, *Moraxella*
- **ATYPICAL**—*Mycoplasma*, *Chlamydia*, *Legionella*, TB, community-acquired MRSA
- **VIRAL**—influenza, parainfluenza, metapneumovirus, RSV, adenovirus
- **FUNGAL**—blastomycosis, cryptococcus, histoplasmosis

ASPIRATION PNEUMONIA

- **POLYBACTERIAL INCLUDING ANAEROBES**—*Bacteroides*, *Peptostreptococcus*, *Fusobacterium* species and other Gram-positive bacilli
- **CHEMICAL PNEUMONITIS**

PNEUMONIA IN THE IMMUNOCOMPROMISED (see p. 291)

NOSOCOMIAL PNEUMONIA—begins in nonintubated patient within 48 hours of admission

- **POLYBACTERIAL**—*Staphylococcus aureus*, MRSA, *Pseudomonas aeruginosa*, Enterobacteriaceae (*Klebsiella*, *Escherichia coli*, *Serratia*), *Haemophilus*, *Acinetobacter*
- **VIRAL**—influenza

VENTILATOR-ASSOCIATED PNEUMONIA—begins >48 hours after the patient is intubated (see p. 107)

HEALTHCARE ASSOCIATED PNEUMONIA—pneumonia that (A) occurs within 90 days of hospitalization of 2 days or more, a stay at nursing home, or a visit to an oral puncture care facility, hospital-based clinic or hemodialysis facility; or (B) occurs within 3 days of receiving antibiotics, chemotherapy, or any type of wound care

PATHOPHYSIOLOGY

COMPLICATIONS OF PNEUMONIA

- **PULMONARY**—ARDS, lung abscess ± cavitary formation, parapneumonic effusion/empyema, pleuritis ± hemorrhage
- **EXTRAPULMONARY**—purulent pericarditis, hyponatremia (from SIADH), sepsis

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE COMMUNITY-ACQUIRED PNEUMONIA?

	LR+	LR–
History		
Cough	1.8	0.31
Sputum	1.3	0.55
Dyspnea	1.4	0.67
Fever	1.7–2.1	0.59–0.71
Asthma	0.1	3.8
Dementia	3.4	0.94
Immunosuppression	2.2	0.85
Physical		
RR >25	1.5–3.4	0.78–0.82
Dullness to percussion	2.2–4.3	0.79–0.93
Decreased breath sounds	2.3–2.5	0.64–0.78
Crackles	1.6–2.7	0.62–0.87
Bronchial breath sounds	3.5	0.9
Egophony	2.0–8.6	0.76–0.96

PREDICTION RULE—Diehr model (rhinorrhea = −2 points, sore throat = −1 point, night sweats = +1 point, myalgias = +1 point, sputum all day = +1 point, RR >25 = +2 points, temp ≥37.8 °C [≥100 °F] = +2 points. If score ≥3, LR 14; if ≥1, LR 5.0; if < −1 LR 0.22)

CLINICAL FEATURES (CONT'D)

APPROACH—"individual or combinations of symptoms and signs have inadequate test characteristics to rule in or rule out the diagnosis of pneumonia. Decision rules that use the presence or absence of several symptoms and signs to modify the probability of pneumonia are available, the simplest of which requires the absence of any vital sign abnormalities to exclude the diagnosis. If diagnostic certainty is required in the management of a patient with suspected pneumonia, then chest radiography (gold standard) should be performed"

JAMA 1997 278:17

***Update: The Rational Clinical Examination.* McGraw-Hill, 2009**

SURFACE LUNG MARKINGS

- **INFERIOR MARGIN OF THE LUNGS**—level of 6th rib at the mid-clavicular line, level of 8th rib at the mid-axillary line, and level of 10th rib at the mid-scapular line
- **OBLIQUE (MAJOR) FISSURES**—draw a line diagonally from T3 vertebral body posteriorly to the 6th rib anteriorly
- **HORIZONTAL (MINOR) FISSURE**—draw a horizontal line at the level of right anterior 4th rib

RELATED TOPICS
Hypoxemia (p. 102)
Parapneumonic Effusion and Empyema (p. 12)
Ventilator-Associated Pneumonia (p. 107)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, troponin/CK, AST, ALT, ALP, bilirubin, urinalysis
- **MICROBIOLOGY**—blood C&S, sputum Gram stain/AFB/C&S/fungal, urine C&S
- **IMAGING**—CXR ± CT chest
- **ABG**—if respiratory distress, and for PSI if deciding on possible hospitalization

SPECIAL

- **BRONCHOSCOPY**
- **NASOPHARYNGEAL SWAB**—if suspect viral infection, check for influenza A/B, parainfluenza, human metapneumovirus, RSV, adenovirus
- **MYCOPLASMA IgM**
- **URINE FOR *LEGIONELLA* ANTIGEN**

DIAGNOSTIC AND PROGNOSTIC ISSUES

PNEUMONIA SEVERITY OF ILLNESS (PSI) SCORE

- **SCORING**—age, female (–10), nursing home (+10), cancer (+30), liver disease (+20), heart failure (+10), CVA (+10), renal failure (+10), altered mental status (+20), RR >30 (+20), SBP <90 mmHg (+20), temp >40°C [>104°F] (+15), HR >125 (+10), pH <7.35 (+30), BUN >10.7 mmol/L [>30 mg/dL] +20, Na <130 mmol/L (+20), glucose >13.9 mmol/L [>250 mg/dL] +10, hematocrit <30% (+10), P_aO_2 <60 mmHg or O_2 saturation <90% on room air (+10), pleural effusion (+10)
- **UTILITY**—originally developed as a prognostic tool. Consider admission if PSI score >90. Clinical judgment more important than PSI in determining admission

NEJM 2002 347:25

MANAGEMENT

ACUTE—ABC, $\mathbf{O_2}$, IV, consider ***salbutamol*** 100 µg MDI 2 puffs q6h + q1h PRN

ANTIBIOTICS

- **COMMUNITY-ACQUIRED PNEUMONIA**—see treatment issues for an approach to selecting the appropriate regimen (remember to adjust for renal function)
  - **TETRACYCLINE**—*doxycycline* 100 mg PO BID × 10 days
  - **MACROLIDES**—*azithromycin* 500 mg PO first day, then 250 mg PO daily × 4 days; *clarithromycin* 250–500 mg PO BID × 10 days
  - **FLUOROQUINOLONES**—*levofloxacin* 500 mg PO daily × 7–10 days (or 750 mg × 5 days), *moxifloxacin* 400 mg PO daily × 10 days; avoid if exposed to fluoroquinolone within last 3–6 months
  - **β-LACTAMS**—*amoxicillin* 1 g PO TID, *amoxicillin–clavulanate* 2 g PO BID, *cefuroxime* 750 mg IV q8h or 500 mg PO BID, *cefotaxime* 1 g IV q8h, *ceftriaxone* 1–2 g IV q24h
  - **ANAEROBIC COVERAGE**—if suspect aspiration, add *clindamycin* 150–450 mg PO q6h or 600–900 mg IV q8h or *metronidazole* 500 mg PO/IV BID–TID
- **NOSOCOMIAL PNEUMONIA**—see treatment issues for an approach to selecting the appropriate regimen
  - **ANTI-PSEUDOMONAL**—ceftazidime, cefepime, meropenem, ciprofloxacin, aminoglycosides, piperacillin–tazobactam (do not use same class of agent when double covering for *Pseudomonas*)

MANAGEMENT (CONT'D)

- **FURTHER GRAM-NEGATIVE COVERAGE**—*ciprofloxacin* 500 mg PO BID, *gentamicin* 6 mg/kg IV q24h, *tobramycin* 6 mg/kg IV q24h (follow levels to adjust dosing)
- **ANAEROBIC COVERAGE**—if suspect aspiration, replace gentamicin with *clindamycin* 150–450 mg PO q6h or 600–900 mg IV q8h or add *metronidazole* 500 mg PO BID
- **ANTIBIOTIC COURSE**—7–8 days for most, 14–21 days for *Pseudomonas*, *Staphylococcus aureus*, *Stenotrophomonas*, and *Acinetobacter*

- **ASPIRATION PNEUMONIA**—*clindamycin* 600 mg IV BID, switch to 300 mg PO QID when stable. May add cefotaxime or ceftriaxone for Gram-positive and Gram-negative coverage
- **TUBERCULOSIS PNEUMONIA**—see p. 279
- **PNEUMOCYSTIS JIROVECI PNEUMONIA**—see p. 291

NON-PHARMACOLOGIC TREATMENTS

- **VACCINATIONS**—influenza vaccine annually and pneumococcal vaccine booster every 5 years
- **CHEST PHYSIOTHERAPY**

TREATMENT ISSUES

IMPORTANT NOTE—avoid using the same antibiotic class if given within 3 months. Consider vancomycin or linezolid if MRSA suspected; emergence of community-acquired MRSA associated with serious necrotizing infections

OUTPATIENT ANTIBIOTICS CHOICE

- **PREVIOUSLY HEALTHY**—macrolide (azithromycin, clarithromycin, or doxycycline). Other antibiotic choices include fluoroquinolone, macrolide plus amoxicillin ± clavulanate
- **COMORBIDITIES** (COPD, diabetes, renal failure, HF, malignancy)—macrolide or fluoroquinolone
- **SUSPECTED ASPIRATION WITH INFECTION**—amoxicillin–clavulanate or clindamycin
- **INFLUENZA WITH BACTERIAL SUPERINFECTION**—β-lactam or fluoroquinolone

INPATIENT ANTIBIOTIC CHOICE—second-third-generation β-lactam plus macrolide or respiratory fluoroquinolone

ICU ANTIBIOTICS CHOICE

- ***PSEUDOMONAS* UNLIKELY**—macrolide plus β-lactam or fluoroquinolone plus β-lactam
- ***PSEUDOMONAS* UNLIKELY BUT β-LACTAM ALLERGY**—fluoroquinolone with or without clindamycin
- ***PSEUDOMONAS* LIKELY**—double coverage with agents that are effective against *Pseudomonas* (different classes)

TREATMENT ISSUES (CONT'D)

- ***PSEUDOMONAS* LIKELY BUT β-LACTAM ALLERGY**—aztreonam plus levofloxacin or aztreonam plus moxifloxacin, with or without aminoglycoside

NURSING HOME ANTIBIOTICS CHOICE

- **TREATMENT IN NURSING HOME**—fluoroquinolone or macrolide plus amoxicillin–clavulanate
- **IN HOSPITAL**—same as inpatient

DISCHARGE DECISION—clinical stabilization usually takes 2–3 days. When symptoms have significantly improved, vital signs are normalized, and patient has defervesced, patients at low risk may be safely discharged on the day of switching to oral therapy without adverse consequences. Time to radiographic resolution is variable, with up to 5 months for pneumococcal pneumonia associated with bacteremia

IDSA Guidelines 2003

SPECIFIC ENTITIES

CAUSES OF NON-RESOLVING PNEUMONIA—**non-infectious** (malignancy especially bronchoalveolar carcinoma or lymphoma, cryptogenic organizing pneumonia, hemorrhage), **non-bacterial** (viral, fungal), **immunocompromised host, antibiotic resistance**, **pneumonia complications** (abscess, empyema, ARDS)

CAUSES OF RECURRENT PNEUMONIA

- **IMMUNOCOMPROMISED ★SADDIST★**—**S**uppressants (steroids, chemotherapy, transplant medications, alcohol), **A**IDS, **D**iabetics, **D**ecreased nutrition, **I**mmunoglobulin (hypogammaglobulinemia), **S**olid organ failure (renal, liver, splenectomy), **T**umors
- **PULMONARY**—bronchiectasis, COPD, cystic fibrosis, abnormal anatomy
- **GI**—aspiration

LUNG ABSCESS

- **CAUSES**—**anaerobes** (*Peptostreptococcus*, *Prevotella*, *Bacteroides*, *Fusobacterium*), **Gram positive** (*S. milleri*, microaerophilic streptococcus, *S. aureus*), **Gram negative** (*Klebsiella*, *Haemophilus*, *Legionella*). Nocardia and actinomycosis can rarely cause lung abscess
- **TREATMENTS**—clindamycin until radiographic improvement and stabilization (usually several weeks to months, can be completed with oral antibiotics once patient is stable). No need for percutaneous drainage. If complicated abscess, consider lobectomy or pneumonectomy

Pulmonary Embolism

NEJM 2008 359:26

PATHOPHYSIOLOGY

VIRCHOW'S TRIAD—risk factors for venous thromboembolism

- **ENDOTHELIAL OR VESSEL WALL INJURY**—fracture of pelvis, femur, or tibia
- **HYPERCOAGUABILITY**—obesity, pregnancy, estrogen, smoking, **cancer** (high suspicion of occult malignancy in patients who develop pulmonary embolism while on anticoagulation), **autoimmune disorders** (antiphospholipid antibody syndrome, lupus anticoagulant, IBD), **genetics** (history of DVT/PE, factor V Leiden, antithrombin III deficiency, protein C/S deficiency, prothrombin G20210A mutation, hyperhomocysteinemia)
- **STASIS**—surgery requiring >30 min of anesthesia, prolonged immobilization, CVA, HF

CLINICAL FEATURES

HISTORY—dyspnea (sudden onset), pleuritic chest pain, cough, hemoptysis, pre/syncope, unilateral leg swelling/pain, past medical history (previous DVT/PE, active cancer, immobilization or surgery in last 4 weeks, miscarriages), medications (birth control pill, anticoagulation)

PHYSICAL—vitals (tachycardia, tachypnea, hypotension, fever, hypoxemia), respiratory examination (pulmonary hypertension if chronic PE), cardiac examination (right heart strain), leg swelling

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE PULMONARY EMBOLISM?

PREDICTION RULES—Wells, PISA-PED, Geneva rule

APPROACH—combining the pretest probability with results of D-dimer testing reduces the need for further investigations in patients with low (<15%) to moderate (15–35%) clinical pretest probability. A patient with low to moderate clinical probability of PE with a normal D-dimer has a LR of 0 (95% CI 0–0.06) for PE. When there is a discrepancy between clinical gestalt and clinical prediction rule, consider placing the patient into the higher pretest probability group

JAMA 2003 290:21

Update: The Rational Clinical Examination. McGraw-Hill, 2009

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, PTT, INR, troponin/CK × 3, D-dimer (if low probability for PE or outpatient), βhCG in women of reproductive age
- **IMAGING**—CXR, duplex US of legs, V/Q scan, CT chest (PE protocol)
- **ECG**—may see normal sinus rhythm (most common), sinus tachycardia (most common abnormality), atrial fibrillation, right ventricular strain (T wave inversion in anterior precordial leads), non-specific ST-T wave changes, right axis deviation, right bundle branch block and/or $S_1Q_3T_3$ (tall S wave in lead I, Q wave and inverted T wave in lead III)
- **ABG**—if respiratory distress

SPECIAL

- **ECHOCARDIOGRAM**—to check for right heart strain (dilated RV and elevated RVSP). Particularly important if hemodynamic changes
- **PULMONARY ANGIOGRAM**—gold standard
- **THROMBOPHILIA WORKUP**—factor V Leiden, prothrombin G20210A, anticardiolipin antibody, lupus anticoagulant, protein C, protein S, antithrombin III, fibrinogen; consider homocysteine level and workup for paroxysmal nocturnal hemoglobinuria and antiphospholipid syndrome in cases of combined arterial–venous thrombosis. Routine testing for hypercoagulable disorders is NOT warranted

DIAGNOSTIC ISSUES

CXR FINDINGS IN PULMONARY EMBOLISM—normal, atelectasis, unilateral small pleural effusion, enlarged central pulmonary artery, elevated hemidiaphragm, Westermark's sign (abrupt truncation of pulmonary vessel), Hampton's hump (wedge infarct)

D-DIMER (sens 85–96%, spc 45–68%, LR+ 1.7–2.7, LR–0.09–0.22)—can rule out PE if low clinical suspicion

V/Q SCAN (sens high, spc high)—result often not definitive (intermediate probability) because of other intraparenchymal abnormalities

CT PE PROTOCOL (sens 57–100%, spc 78–100%)—can be very helpful as it provides clues to other potential diagnoses/pathologies as well

DIAGNOSTIC ISSUES (CONT'D)

LEG VEIN DOPPLER (sens 50%, spc moderate)—serial dopplers may be used for diagnosis of DVT if CT or V/Q scan failed to demonstrate PE but clinical suspicion still high

WELL'S CRITERIA FOR PULMONARY EMBOLISM

- **SCORING**—signs/symptoms of DVT (+3), alternative diagnosis less likely (+3), HR >100 (+1.5), immobilization or surgery in last 4 weeks (+1.5), previous DVT/PE (+1.5), hemoptysis (+1), active cancer (+1)
- **LOW SUSPICION** (sum 0–1, <10% chance)—D-dimer → if positive, CT or V/Q scan
- **INTERMEDIATE SUSPICION** (sum 2–6, 30% chance)—D-dimer → CT or V/Q scan → if negative but suspicious, leg doppler → if negative but still suspicious, pulmonary angiogram
- **HIGH SUSPICION** (sum >6, >70% chance)—CT or V/Q scan → if negative but suspicious, leg doppler → if negative but still suspicious, pulmonary angiogram

NEJM 2003 349:13

Related Topics
Anticoagulation Therapy (p. 178)
DVT (p. 176)
Hypercoagulable States (p. 173)
Pulmonary Embolism in Pregnancy (p. 469)

MANAGEMENT

ACUTE—ABC, O_2 to keep sat >94%, IV, consider thrombolysis (must be done in ICU) for massive PE (hemodynamic instability, right ventricular strain)

ANTICOAGULATION—if moderate to high risk of developing PE, consider initiating anticoagulation while waiting for investigations. **Heparin** (*unfractionated heparin* 5,000 U IV bolus, then 1,000 U/h and adjust to 1.5–2.5× normal PTT; use UFH if considering thrombolysis), **LMWH** (*enoxaparin* 1 mg/kg SC BID or 1.5 mg/kg SC daily, *tinzaparin* 175 U/kg SC daily), or **fondaparinux** 5 mg SC daily (<50 kg), 7.5 mg SC daily (50–100 kg), or 10 mg SC daily (>100 kg). Start ***warfarin*** 5 mg PO daily within 48 h and continue heparin/LMWH/fondaparinux for at least 5 days and until INR is between 2 and 3 for at least 48 h. Factor Xa inhibitors (rivaroxaban, apixaban) and direct thrombin inhibitors (dabigatran) not recommended for initial treatment of hemodynamically unstable PE; may consider in stable patients under supervision of physician familiar with novel anticoagulant therapy

MANAGEMENT (CONT'D)

THROMBOLYTICS—controversial as increased risk of intracranial bleed and multiple contraindications (see below). Consider only if hemodynamically unstable or life-threatening pulmonary embolism. *TPA* 100 mg IV over 2 h, or *streptokinase* 250,000 IU over 30 min, the 100,000 IU/h over 12–24 h or 1.5 million IU over 2 h. Unfractionated heparin may be used concurrently

SURGICAL—embolectomy. Consider if thrombolysis failed or contraindicated or if hemodynamically unstable

IVC FILTER—if anticoagulation contraindicated

TREATMENT ISSUES

CONTRAINDICATIONS TO THROMBOLYTIC THERAPY

- **ABSOLUTE CONTRAINDICATIONS**—history of hemorrhagic stroke or stroke of unknown origin, ischemic stroke in previous 3 months, malignant intracranial neoplasm, suspected aortic dissection, active bleeding, major trauma in previous 2 months, intracranial surgery or head injury within 3 weeks
- **RELATIVE CONTRAINDICATIONS**—TIA within 6 months, oral anticoagulation, pregnancy or within 1 week postpartum, non-compressible puncture sites, traumatic/prolonged (>10 min) CPR, uncontrolled hypertension (SBP >185 mmHg, DBP >110 mmHg), recent bleeding (<2–4 weeks), current use of anticoagulants, advanced liver disease, infective endocarditis, active peptic ulcer, thrombocytopenia

ANTICOAGULATION DURATION

- **FIRST PULMONARY EMBOLISM WITH REVERSIBLE OR TIME-LIMITED RISK FACTOR**—anticoagulation for at least 3 months
- **UNPROVOKED PE**—at least 3 months of treatment. If no obvious risk factors for bleeding, consider indefinite anticoagulation
- **PE AND MALIGNANCY**—treatment with SC LMWH better than oral warfarin. Treatment should be continued until eradication of cancer as long as there are no significant contraindications to anticoagulation
- **PE AND PREGNANCY**—SC LMWH is preferred for outpatient treatment. Total duration of therapy should be 6 months unless patient has risk factors for hypercoagulable state

Chest 2012; 141: 2 Suppl

SPECIFIC ENTITIES

FAT EMBOLISM

- **PATHOPHYSIOLOGY**—embolism of fat globules to lungs, brain, and other organs → metabolized to fatty acids leading to inflammatory response. Commonly caused by closed fractures of long bones, but may also occur with pelvic fractures, orthopedic procedures, bone marrow harvest, bone tumor lysis, osteomyelitis, liposuction, fatty liver, pancreatitis, and sickle cell disease
- **CLINICAL FEATURES**—triad of dyspnea, neurological abnormalities (confusion), and petechial rash (head and neck, chest, axilla). May also have fever, thrombocytopenia, and DIC
- **DIAGNOSIS**—clinical diagnosis (rash is pathognomonic). Investigations may include CXR, V/Q scan, CT chest, and MRI head
- **TREATMENTS**—supportive care as most patients will fully recover. Mortality is 10%. Primary prophylaxis includes early mobilization. Consider trial of systemic steroids

Pleural Effusion

NEJM 2002 346:25

DIFFERENTIAL DIAGNOSIS

EXUDATIVE—malignancy, infections, connective tissue disease, hypothyroidism, pulmonary embolism, hemothorax, pancreatitis, chylothorax, trapped lung

TRANSUDATIVE—HF, hypoalbuminemia (GI losing enteropathy, cirrhosis, nephrotic syndrome, malnutrition), SVC obstruction, hepatohydrothorax, urinothorax, atelectasis, trapped lung, peritoneal dialysis, hypothyroidism, pulmonary embolism

NOTE: pulmonary embolism, malignancy, hypothyroidism, trapped lung, SVC obstruction, and sarcoidosis are usually exudative, but can occasionally be transudative. HF following diuresis may become "pseudo-exudative"

CLINICAL FEATURES

HISTORY—dyspnea, cough, hemoptysis, chest pain, weight loss, fever, trauma, occupational exposures, past medical history (pneumonia, liver disease, kidney disease, thyroid disease, cancer, HF, thromboembolic disease, connective tissue disease, smoking), medications

PHYSICAL—vitals, cyanosis, clubbing, tracheal deviation away from side of effusion (if no collapse or trapped lung), peripheral lymphadenopathy, Horner's syndrome, respiratory examination (decreased breath sounds and tactile fremitus, stony dullness to percussion), cardiac examination, leg swelling (HF or DVT)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THE PATIENT HAVE PLEURAL EFFUSION?

	Sens	Spc	LR+	LR–
Physical				
Asymmetric chest expansion	74%	91%	8.1	0.29
Auscultatory percussion	77%	92%	7.7	0.27
Crackles	56%	62%	1.5	0.71
Diminished breath sounds	42–88%	83–90%	4.3–5.2	0.15–0.64
Dullness to conventional percussion	73%	91%	8.7	0.31
Pleural friction rub	5.30%	99%	3.9	0.96
Reduced tactile fremitus	82%	86%	5.7	0.21
Reduced vocal resonance	76%	88%	6.5	0.27

AUSCULTATORY PERCUSSION—auscultate with the diaphragm of the stethoscope over the posterior chest wall while gently tapping over the manubrium with the distal phalanx of one finger. Diminished resonance suggests effusion

APPROACH—"dullness to percussion and tactile fremitus are the most useful findings for pleural effusion. Dull chest percussion makes the probability of a pleural effusion much more likely but still requires a CXR to confirm the diagnosis. When the pretest probability of pleural effusion is low, the absence of reduced tactile fremitus makes pleural effusion less likely so that a CXR might not be necessary depending on the overall clinical situation"

JAMA 2009 301:3

CLINICAL FEATURES (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE AN EXUDATIVE PLEURAL EFFUSION?

	Sens	Spc	LR+	LR–
Pleural cholesterol >55 mg/dL	85–94%	95–99%	7.1–250	0.07–0.16
Pleural LDH >200 U/L	70%	98%	18	0.32
Pleural: serum cholesterol ratio >0.3	93%	94%	14	0.08
Pleural: serum LDH ratio >0.6	88%	91%	9.2	0.14
Pleural: serum protein ratio >0.5	90%	90%	7.0	0.12
Combined ≥1 of Light's criteria	97%	85%	5.2	0.04
Pleural protein >3 g/dL	88%	86%	5.1	0.14
Pleural LDH >2/3 upper limit of normal	88–89%	93–100%	1.7–13	0.23–0.26
Serum: pleural albumin gradient <1.2 mg/dL	86–95%	42–100%	1.5–36	0.06–0.32

APPROACH—effusions meeting none of Light's criteria are most likely transudative. However, if the effusion meets Light's criteria or if the effusion has a pleural cholesterol >55 mg/dL, pleural LDH >200 U/L, or ratio of pleural cholesterol to serum cholesterol >0.3, the effusion is likely exudative

JAMA 2014 311:23

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, LDH, total protein, AST, ALT, ALP, bilirubin, INR, PTT, albumin
- **IMAGING**—CXR (PA, lateral, decubitus), CT chest
- **THORACENTESIS**—send pleural fluid for cell count and differential, Gram stain, C&S, AFB and fungal cultures, LDH, total protein, pH, and cytology. Under special circumstances, also consider amylase, glucose, cholesterol, adenosine deaminase (for TB), albumin

SPECIAL

- **BIOPSY**—closed pleural biopsy, medical thoracoscopy, bronchoscopy, surgical biopsy (video-assisted thoracic surgery)

DIAGNOSTIC ISSUES

OVERALL APPROACH—generally, if the effusion is >1/4 of hemithorax, enough fluid is present for diagnostic thoracentesis. US-guided thoracentesis is standard of care. If only a small amount of fluid is present (<10 mm [<0.4 in.]) and/or HF suspected, start with diuresis for 2–3 days. If no improvement, perform thoracentesis to distinguish between transudative and exudative causes

LIGHT'S CRITERIA FOR EXUDATIVE EFFUSION—any one of the following criteria would suggest exudative effusion: fluid/serum total protein ratio >0.5, fluid/serum LDH ratio >0.6, fluid LDH >2/3 upper limit of normal serum level

THORACENTESIS PROCEDURE—see **NEJM 2006 355:e16**

DIAGNOSTIC ISSUES (CONT'D)

PLEURAL FLUID ANALYSIS

- **FLUID ACIDOSIS** (pH <7.2)—complicated parapneumonic, TB, paragonimiasis, malignancy, rheumatoid arthritis, SLE, hemothorax, esophageal rupture
- **FLUID GLUCOSE** (<3.3 mmol/L [<60 mg/dL])—parapneumonic, TB, paragonimiasis, malignancy, rheumatoid arthritis, Churg–Strauss, hemothorax
- **FLUID EOSINOPHILIA** (>10%)—paragonimiasis, malignancy, Churg–Strauss, asbestos, drug reaction, pulmonary embolism, hemothorax, pneumothorax, idiopathic (20%)
- **CYTOLOGY FOR MALIGNANCY**—the yield for diagnosis with single attempt is 60%, two attempts is 85%, three attempts is 90–95%; obtain as much fluid as possible to increase diagnostic yield
- **FLUID FOR AFB**—obtain as much fluid as possible and ask laboratory to centrifuge collection and to culture sediment to increase diagnostic yield

MANAGEMENT

SYMPTOM CONTROL—**O_2**, **diuresis** (furosemide), **drainage** (thoracentesis, pigtail catheter, PleurX catheter, chest tube), **pleurodesis** (talc slurry or poudrage), **surgery** (talc slurry, pleuroperitoneal shunt, pleural abrasion, pleurectomy)

TREAT UNDERLYING CAUSE

SPECIFIC ENTITIES

PARAPNEUMONIC EFFUSION

- **UNCOMPLICATED**—exudative effusion that resolves with resolution of pneumonia. Generally disappears with antibiotics alone

SPECIFIC ENTITIES (CONT'D)

- **COMPLICATED**—persistent bacterial invasion and fluid collection. Characterized by pleural fluid acidosis but sterile fluid. Pleural loculation may occur as fibrin gets deposited from inflammation. Treated the same as empyema
- **EMPYEMA**—presence of bacteria in Gram stain or pus in drainage (culture not necessary). pH often <7.2. For unloculated fluid, chest tube/small-bore catheter drainage usually adequate. For loculated effusions, intrapleural thrombolytics (streptokinase or TPA) and DNase could be considered. Thoracoscopy represents an alternative to fibrinolytics. Open decortication is the last resort

SPECIFIC ENTITIES (CONT'D)

TRAPPED LUNG—stable chronic effusion, especially with history of pneumonia, pneumothorax, thoracic surgery or hemothorax. Diagnosis is established by measuring negative change in intrapleural pressure during thoracentesis. Depending on chronicity, treat by lung re-expansion. Thoracotomy with decortication sometimes required in infectious cases

HEPATOHYDROTHORAX—suspect if cirrhosis and portal hypertension, even in the absence of ascites. Pleural effusion results from passage of peritoneal fluid into pleura because of negative intrathoracic pressures and diaphragmatic defects. Do not insert chest tube. Treat with diuresis, salt restriction, and consider liver transplantation/TIPS procedure

Chronic Cough

DIFFERENTIAL DIAGNOSIS

NON-PULMONARY—GERD, ACE inhibitors, occult congestive heart failure

PULMONARY

- **AIRWAY**—post-nasal drip/upper airway cough syndrome, asthma, chronic bronchitis, non-asthmatic eosinophilic bronchitis, bronchiectasis, neoplasm, foreign body, post-viral
- **PARENCHYMA**—occult infection, occult aspiration, interstitial lung disease, lung abscess
- **VASCULAR**—early pulmonary hypertension

INVESTIGATIONS

BASIC

- **MICROBIOLOGY**—sputum Gram stain/AFB/C&S
- **IMAGING**—CXR (order inspiratory and expiratory views if foreign body aspiration or endobronchial lesion suspected)
- **SPIROMETRY/PFT**

SPECIAL

- **SINUS IMAGING**
- **METHACHOLINE CHALLENGE**
- **ESOPHAGEAL PH MONITORING**

PATHOPHYSIOLOGY

DEFINITION OF CHRONIC COUGH— > 3 weeks

COMPLICATIONS OF CHRONIC COUGH—exhaustion, insomnia, anxiety, headaches, dizziness, hoarseness, musculoskeletal pain, urinary incontinence, abdominal hernias

COUGH REFLEX

- **AFFERENT**—chemical or mechanical stimuli → cough receptors in the epithelium of the upper and lower respiratory tracts, pericardium, esophagus, diaphragm, and stomach → afferent nerves (vagus, glossopharyngeal, trigeminal, and phrenic) → cough center in the medulla
- **EFFERENT**—cough center with cortical input → efferent signals travel down the vagus, phrenic, and spinal motor nerves → expiratory muscles → cough

MANAGEMENT

SYMPTOM CONTROL—*codeine* 20 mg PO q4h PRN, *dextromethorphan* 20 mg PO q4h PRN

TREAT UNDERLYING CAUSE—switch to ARB if ACE inhibitor suspected as cause of chronic cough

CHEST 2006 129:1 Suppl

SPECIFIC ENTITIES

POST-NASAL DRIP/UPPER AIRWAY COUGH SYNDROME

- **PATHOPHYSIOLOGY**—secretions in the upper airway stimulate cough receptors within the pharyngeal or laryngeal mucosa
- **CAUSES**—allergic, perennial non-allergic rhinitis, vasomotor rhinitis, acute nasopharyngitis, sinusitis

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—non-specific findings; consider sinus imaging
- **TREATMENTS**—reduce irritant exposure, antihistamine-decongestant combinations (*diphenhydramine* 25–50 mg PO q4–6 h PRN, pseudoephedrine, *ipratropium nasal spray* 0.03% 2 sprays/nostril BID–TID, nasal corticosteroids, nasal saline rinses BID), surgical correction for anatomical abnormalities

Hemoptysis

DIFFERENTIAL DIAGNOSIS

NON-CARDIOPULMONARY—epistaxis, upper GI bleed, coagulopathy

CARDIAC—HF, mitral stenosis

PULMONARY

- **AIRWAY**—bronchitis (acute, chronic), bronchiectasis, malignancy, foreign body, trauma
- **PARENCHYMA**
  - **MALIGNANCY**—lung cancer, metastasis
  - **INFECTIONS**—necrotizing pneumonia (*Staphylococcus, Pseudomonas*), abscess, septic emboli, TB, fungal
  - **ALVEOLAR HEMORRHAGE**—granulomatosis with polyangiitis (Wegener's), Churg–Strauss, Goodpasture disease, pulmonary capillaritis, connective tissue disease
- **VASCULAR**—pulmonary embolism, pulmonary hypertension, AVM, iatrogenic

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, INR, PTT, urinalysis
- **MICROBIOLOGY**—blood C&S, sputum Gram stain/C&S/AFB/fungal/cytology
- **IMAGING**—CXR, CT chest (warranted in most patients unless obvious explanation)
- **BRONCHOSCOPY**—warranted in most patients unless obvious explanation

SPECIAL

- **ETIOLOGY WORKUP**—ANA, p-ANCA (myeloperoxidase MPO antibodies), c-ANCA (antiproteinase-3 PR3 antibodies), anti-GBM antibody, rheumatologic screen (extractable nuclear antigens)
- **ABG**—if respiratory distress

PATHOPHYSIOLOGY

MASSIVE HEMOPTYSIS—100–600 mL blood in 24 h. Patients may die of asphyxiation (rather than exsanguination)

CLINICAL FEATURES

HISTORY—characterize hemoptysis (amount, frequency, previous history), cough (productive), dyspnea, chest pain, epistaxis, hematemesis, weight loss, fever, night sweats, exposure, travel, joint inflammation, rash, visual changes, past medical history (smoking, lung cancer, TB, thromboembolic disease, cardiac disease), medications (warfarin, ASA, NSAIDs, natural supplements)

PHYSICAL—vitals, weight loss, clubbing, cyanosis, lymphadenopathy, Horner's syndrome, respiratory and cardiac examination, leg swelling (HF or DVT), joint examination, skin examination

MANAGEMENT

ACUTE—ABC, **O_2**, **IV**, **intubation** to protect airway if significant hemoptysis (with double lumen tube if available), position patient in lateral decubitus position with affected lung on bottom (to preserve non-affected lung on top)

SYMPTOM CONTROL—cough suppressants, sedatives, stool softeners. **Transfusions**. Urgent interventional **bronchoscopy** (cold saline, topical epinephrine, cautery, airway blocker, double lumen endotracheal tube). **Angiographic arterial embolization. Lung resection**

TREAT UNDERLYING CAUSE—**correct coagulopathy** (*vitamin K* 10 mg SC/IV × 1 dose or FFP); **antibiotics**; **radiation** for tumors; **diuresis** for HF; **immunosuppression** for vasculitis

SPECIFIC ENTITIES

GOODPASTURE DISEASE

- **PATHOPHYSIOLOGY**—anti-glomerular basement membrane antibodies → attack pulmonary and renal basement membrane

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—hemoptysis and hematuria, with respiratory and renal failure if severe
- **DIAGNOSIS**—lung/kidney biopsy
- **TREATMENTS**—steroids, cyclophosphamide, plasmapheresis

Solitary Pulmonary Nodule — NEJM 2003 348:25

DIFFERENTIAL DIAGNOSIS

MALIGNANT—bronchogenic, carcinoid, metastatic cancer

BENIGN—healed infectious granuloma, benign tumors (hamartoma), AVM, rheumatoid nodule, granulomatosis with polyangiitis (GPA), hydatid cyst, round atelectasis, intra-pulmonary lymph nodes, pseudotumor

CLINICAL FEATURES

HISTORY—dyspnea, cough, hemoptysis, wheezing, chest pain, weight loss, fever, night sweats, rheumatologic screen, past travel history, occupational exposures, medical history (smoking, lung cancer or other malignancies, TB, infections, rheumatoid arthritis), medications

PHYSICAL—vitals, weight loss, clubbing, cyanosis, Horner's syndrome, SVC syndrome, lymphadenopathy, respiratory examination, abdominal examination (hepatomegaly), bony tenderness

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, LDH, AST, ALT, ALP, bilirubin, INR, PTT
- **IMAGING**—old films (2 years ago for comparison), CXR, CT chest

SPECIAL

- **ABG**
- **SCREENING FOR INFLAMMATORY DISORDERS**—ESR, CRP, ANA, ANCA
- **BIOPSY**—bronchoscopy or CT guided
- **PET/CT SCAN**—if moderate to high suspicion of lung cancer

DIAGNOSTIC ISSUES

FINDINGS SUGGESTIVE OF MALIGNANCY

★ABCD★

- **A**ge >50
- **B**order—irregular, nodular cavity with thick wall, or spiculation

DIAGNOSTIC ISSUES (CONT'D)

- **C**alcification—eccentric or noncalcified
- **D**iameter >3 cm [>1.2 in.]. If <3 cm, 20–50% malignant. If ≥3 cm, 50% malignant

TIMING—if malignant, usually able to detect an increase in size of SPN between 30 days and 2 years. Unlikely to be malignant if significant change in <30 days or no change in 2 years

CALCIFICATION CLUES

- **MALIGNANCY**—eccentric calcification or noncalcified
- **TUBERCULOSIS OR HISTOPLASMOSIS**—central/complete calcification
- **BENIGN HAMARTOMA**—popcorn calcification

MANAGEMENT

TREAT UNDERLYING CAUSE—if **low probability**, observation with serial CT scans. If **medium probability**, bronchoscopy with biopsy/brush or transthoracic (CT/US-guided) biopsy. If **high probability**, thoracotomy with resection or video-assisted thoracoscopy (for patients who cannot tolerate thoracotomy medically and physiologically)

SPECIFIC ENTITIES

PANCOAST TUMOR

- **PATHOPHYSIOLOGY**—superior sulcus tumors (mostly squamous cell carcinoma) invading and compressing the paravertebral sympathetic chain and brachial plexus
- **CLINICAL FEATURES**—shoulder and arm pain (C8, T1, T2 distribution), **Horner's syndrome** (upper lid ptosis, lower lid inverse ptosis, miosis, anhydrosis, enophthalmos, loss of ciliary-spinal reflex), and neurological symptoms in the arm (intrinsic muscles weakness and atrophy, pain and paresthesia of 4th and 5th digit). Other associated findings include clubbing, lymphadenopathy, phrenic or recurrent laryngeal nerve palsy, and superior vena cava syndrome

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—CXR, CT chest, percutaneous core biopsy
- **TREATMENTS**—concurrent chemoradiotherapy

THORACIC OUTLET OBSTRUCTION

- **PATHOPHYSIOLOGY**—obstruction of the neurovascular bundle supplying the arm at the superior aperture of the thorax. Common structures affected include the brachial plexus (C8/T1 > C5/C6/C7, 95%), subclavian vein (4%), and subclavian artery (1%)
- **CAUSES**—**anatomic** (cervical ribs, congenital bands, subclavicular artery aneurysm), **repetitive hyperabduction/trauma** (hyperextension injury, painters, musicians), **neoplasm** (supraclavicular lymphadenopathy)
- **CLINICAL FEATURES**—triad of numbness, swelling and weakness of the affected upper limb, particularly when carrying heavy objects. Brittle finger nails, Raynaud's, thenar wasting and weakness, sensory loss, decreased radial and brachial pulses, pallor of limb with elevation, upper limb atrophy, drooping shoulders, supraclavicular and infraclavicular lymphadenopathy. Specific maneuvers include **Roos test** (repeatedly clench and unclench fists with arms abducted and externally rotated), **modified Adson's maneuver** (Valsalva maneuver with the neck fully extended, affected arm elevated, and the chin turned away from the involved side), **costoclavicular maneuver** (shoulders thrust backward and downward), **hyperabduction maneuver** (raise hands above head with elbows flexed and extending out laterally from the body), and **Tinel's maneuver** (light percussion of brachial plexus in supraclavicular fossa reproduces symptoms)
- **DIAGNOSIS**—cervical spine films, CXR, MRI
- **TREATMENTS**—conservative (keep arms down at night, avoiding hyperabduction), surgery

RELATED TOPICS
Lung Cancer (p. 203)
SVC Syndrome (p. 253)

Pulmonary Hypertension NEJM 2004 351:15

WHO CLASSIFICATION OF PULMONARY HYPERTENSION

GROUP I. PULMONARY ARTERIAL HYPERTENSION

- **IDIOPATHIC**—primary
- **FAMILIAL AND RELATED DISORDERS**—collagen vascular disease, congenital systemic-to-pulmonary shunts, portal hypertension, HIV, drugs and toxins, thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy
- **ASSOCIATED WITH SIGNIFICANT VENOUS OR CAPILLARY INVOLVEMENT**—pulmonary veno-occlusive disease, pulmonary–capillary hemangiomatosis
- **PERSISTENT PULMONARY HYPERTENSION OF NEWBORN**

GROUP II. PULMONARY VENOUS HYPERTENSION—left-sided atrial or ventricular heart disease, left-sided valvular heart disease

WHO CLASSIFICATION OF PULMONARY HYPERTENSION (CONT'D)

GROUP III. PULMONARY HYPERTENSION ASSOCIATED WITH HYPOXEMIA—COPD, interstitial lung disease, sleep-disordered breathing, alveolar hypoventilation disorders, chronic exposure to high altitude, developmental abnormalities

GROUP IV. PULMONARY HYPERTENSION DUE TO CHRONIC THROMBOTIC DISEASE, EMBOLIC DISEASE, OR BOTH—thromboembolic obstruction of proximal pulmonary arteries, thromboembolic obstruction of distal pulmonary arteries, pulmonary embolism (tumor, parasites, foreign material)

GROUP V. MISCELLANEOUS—sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

PATHOPHYSIOLOGY

DEFINITION OF PULMONARY HYPERTENSION—mean pulmonary arterial pressure (PAP) >25 mmHg at rest or mean PAP >30 mmHg with exercise measured with right heart catheterization

CLINICAL FEATURES

HISTORY—unexplained dyspnea on exertion, cough, chest pain, hemoptysis, dizziness, syncope, hoarseness, past medical history (cardiac and respiratory diseases, thromboembolic diseases, HIV, cirrhosis, autoimmune and rheumatologic disorders), medications (amphetamine, diet pill such as dexfenfluramine)

PHYSICAL—vitals (tachypnea, tachycardia, atrial fibrillation, hypoxemia), peripheral cyanosis, small pulse volume, elevated JVP (prominent a wave or absent if atrial fibrillation, large v wave), right ventricular heave, loud or palpable P2, right-sided S4, tricuspid regurgitation murmur, Graham Steell murmur (high-pitched, decrescendo diastolic rumble over LUSB), crackles, congestive liver, ascites, ankle edema

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, albumin, ANA, RF, anti-CCP, anti-Scl-70, anticentromere antibody, ESR, HIV serology, TSH

INVESTIGATIONS (CONT'D)

- **IMAGING**—CXR, CT chest, V/Q scan or CT chest PE protocol, echocardiogram
- **ECG**
- **OVERNIGHT POLYSOMNOGRAPHY**—if suspect OSA
- **ABG**
- **PFT**

SPECIAL

- **RIGHT HEART CATHETERIZATION WITH VASOREACTIVITY TESTING**

MANAGEMENT

SYMPTOM CONTROL—**diuretics**, **O_2**, **anticoagulation**, **calcium channel blockers** if positive vasoreactivity test (in high doses), **endothelin receptor antagonists** (bosentan), **phosphodiesterase type-5 inhibitors** (sildenafil), prostanoids, soluble guanylate cyclase stimulant

TREAT UNDERLYING CAUSE

ATRIAL SEPTOSTOMY

LUNG TRANSPLANT

Chest 2014 146:2

SPECIFIC ENTITIES

EISENMENGER SYNDROME—left-to-right shunt leading to pulmonary hypertension and eventually right-to-left shunt

Interstitial Lung Disease

DIFFERENTIAL DIAGNOSIS

PRIMARY (idiopathic)—usual interstitial pneumonia (UIP), respiratory bronchiolitis-associated interstitial lung disease (RBILD), desquamative interstitial pneumonia (DIP), acute interstitial pneumonia (AIP), non-specific interstitial pneumonia (NSIP), lymphoid interstitial pneumonia (LIP), cryptogenic organizing pneumonia (COP)

SECONDARY ★DICE★

- **DRUGS**—chemotherapy (bleomycin), sulfa, penicillin, sulfonylurea, gold, penicillamine, phenytoin, amiodarone, nitrofurantoin
- **INFILTRATIVE**—lymphangitic carcinomatosis, sarcoidosis
- **INFECTIONS**—TB, histoplasmosis, coccidioidomycosis
- **INFLAMMATORY**—rheumatoid arthritis, SLE, scleroderma, ankylosing spondylitis, myositis
- **CONGESTIVE HEART FAILURE**

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **ENVIRONMENT**—**organic dust** (hypersensitivity pneumonitis), **inorganic dust** (asbestos, silica, beryllium, coal worker's pneumoconiosis)
- **EOSINOPHILIA-ASSOCIATED PULMONARY INFILTRATES**—allergic bronchopulmonary aspergillosis (ABPA), parasitic, drugs
- **ETC**—pulmonary histiocytosis X, idiopathic pulmonary hemosiderosis, lymphangioleiomyomatosis, radiation

CLINICAL FEATURES

HISTORY—dyspnea (duration, progression), cough, hemoptysis, wheezes, chest pain, impaired exercise tolerance, occupational history (details of all previous jobs, exposure to gases or chemicals particularly important), environmental exposure (home setting, air-conditioning, pets, hobbies),

CLINICAL FEATURES (CONT'D)

rash, joint swelling, past medical history (smoking), medications, family history

PHYSICAL—vitals (tachypnea, hypoxemia), cyanosis, clubbing (idiopathic pulmonary fibrosis, asbestosis, rheumatoid lung, fibrosing NSIP), decreased chest expansion, crackles (fine), wheezes, cor pulmonale. Note that sarcoidosis and silicosis may have a normal lung examination

Related Topics

Allergic Bronchopulmonary Aspergillosis (p. 3)
Restrictive Lung Disease (p. 25)
Rheumatoid Arthritis (p. 314)
Sarcoidosis (p. 482)
Tuberculosis (p. 279)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, ANA, RF, anti-CCP antibody, anti-Scl-70, anticentromere antibody, anti-Jo-1 antibody
- **IMAGING**—CXR, CT chest (high resolution), echocardiogram (if suspect pulmonary hypertension)
- **ABG**
- **PFT**

SPECIAL

- **BIOPSY**—bronchoscopy (transbronchial biopsy), open lung biopsy

DIAGNOSTIC ISSUES

CHARACTERISTIC CXR PATTERNS FOR INTERSTITIAL LUNG DISEASE

- **UPPER LOBE PREDOMINANCE**—sarcoidosis, hypersensitivity pneumonitis, pneumoconiosis, silicosis, histiocytosis X, PJP, ankylosing spondylitis, ABPA, TB
- **LOWER LOBE PREDOMINANCE**—idiopathic pulmonary fibrosis, asbestosis, rheumatoid arthritis, scleroderma, drugs
- **BILATERAL HILAR/MEDIASTINAL ADENOPATHY WITH INTERSTITIAL INFILTRATES**—sarcoidosis, berylliosis, lymphangitic carcinomatosis, TB, fungal, lymphoma
- **EGGSHELL CALCIFICATION OF HILAR/MEDIASTINAL LYMPH NODES**—silicosis (other pneumoconiosis), TB, fungal
- **CALCIFIED PLEURAL PLAQUES**—asbestos

DIAGNOSTIC ISSUES (CONT'D)

- **PLEURAL EFFUSIONS WITH INTERSTITIAL INFILTRATES**—HF, lymphangitic carcinomatosis, rheumatoid arthritis, SLE

MANAGEMENT

TREAT UNDERLYING CAUSE—sarcoidosis (if ≥ stage II or symptomatic, give steroids for at least 6 months, even with improvement of symptoms. See p. 482 for details)

LUNG TRANSPLANT

SPECIFIC ENTITIES

IDIOPATHIC PULMONARY FIBROSIS (IPF)

- **PATHOPHYSIOLOGY**—unknown. Fibrotic rather than inflammatory process; associated with histopathological and/or radiological pattern of usual interstitial pneumonia (UIP)
- **DIAGNOSIS**—CT chest (honeycombing, interlobular septal thickening, traction bronchiectasis, peripheral, sub-pleural, lack of ground glass pattern), bronchoscopy (to rule out other causes, mostly infectious); consider open lung biopsy if CT is not consistent with above
- **TREATMENTS**—referral for lung transplantation should be done early; consider pirfenidone or nintedanib for mild to moderate disease. Systemic steroids ineffective

CMAJ 2004 171:2
Am J Respir Crit Care Med 2011 183:6
NEJM 2014 370:22

HYPERSENSITIVITY PNEUMONITIS

- **PATHOPHYSIOLOGY**—inhaled organic antigens → immune response → acute, subacute, or chronic granulomatous pneumonia
- **DIAGNOSIS**—**major criteria** (compatible symptoms, antigen exposure, imaging findings, lavage lymphocytosis, histologic findings (poorly formed granulomas), reexposure triggers symptoms); **minor criteria** (bilateral crackles, ↓ DLCO, hypoxemia). Combination of major and minor criteria will help raise suspicion of hypersensitivity pneumonitis. Serology may be helpful
- **TREATMENTS**—cessation of exposure, steroids

CRYPTOGENIC ORGANIZING PNEUMONIA (COP)—previously known as bronchiolitis obliterans organizing pneumonia (BOOP)

- **CAUSES**—**idiopathic** (80%), **post-infectious** (CMV, influenza, adenovirus, Chlamydia), **drugs** (amiodarone, bleomycin, gold, sulfasalazine, cephalosporin, cocaine), **connective tissue disease** (RA, SLE, scleroderma, Sjogren's, dermatomyositis), **immunologic** (essential

SPECIFIC ENTITIES (CONT'D)

mixed cryoglobulinemia), **transplantation** (bone marrow, lung, kidney), **malignancy** (MDS, lymphoproliferative diseases, radiation)

- **CLINICAL FEATURES**—about 50% of cases preceded by viral-like respiratory infection. Symptoms include dyspnea on exertion, persistent non-productive cough, and weight loss

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—characteristic findings on CXR and CT chest include bilateral, diffuse, ill-defined alveolar opacities distributed peripherally. PFT shows mainly restrictive lung disease pattern
- **TREATMENTS**—*prednisone* 1 mg/kg PO daily

Obstructive Sleep Apnea NEJM 2007 356:17

DIFFERENTIAL DIAGNOSIS OF SLEEP DISORDERS

HYPERSOMNOLENCE

- **SLEEP DISRUPTION**—obstructive sleep apnea (OSA), periodic limb movement disorder
- **INADEQUATE SLEEP TIME**—medicine residents, shift workers
- **INCREASED SLEEP DRIVE**—narcolepsy, primary CNS hypersomnolence, head injury, severe depression, medications

INSOMNIA

- **ACUTE**—stress, travel through time zones, illness, medications (steroids), illicit drugs (stimulants)
- **CHRONIC**—conditioned, psychiatric disorders, poor sleep hygiene, medical disorders, pain, restless leg syndrome, circadian rhythm disorder

PARASOMNIA—sleep walking, sleep terrors, nocturnal seizures, rapid eye movement behavior disorder

PATHOPHYSIOLOGY

ABNORMAL PHARYNX ANATOMY—decreased upper airway muscle tone and reduced reflexes protecting pharynx from collapse, increased hypercapnic set point → airway collapse with hypoxemia and hypercapnia → partial collapse leads to snoring and hypopnea, full collapse leads to apnea → terminated with arousal → repeated arousals lead to hypersomnolence. Severe chronic hypoxemia leads to pulmonary hypertension

ASSOCIATIONS—obesity, hypothyroidism, acromegaly, amyloidosis, neuromuscular disease, vocal cord paralysis, nasopharyngeal carcinoma, Down syndrome (macroglossia)

PATHOPHYSIOLOGY (CONT'D)

COMPLICATIONS—hypertension, pulmonary hypertension, CAD, CVA, increased motor vehicle accidents

Related Topics
CPAP (p. 105)
Hypertension (p. 65)
Pulmonary Hypertension (p. 17)

CLINICAL FEATURES

HISTORY—daytime sleepiness, habitual snoring, witnessed apneic episodes, poor sleep hygiene, morning headaches, fall asleep while driving, dyspnea, cough, exercise capacity, short-term memory loss, excessive caffeine intake, alcohol intake, past medical history (weight gain, thyroid disease, neurological disease), and medications. The Epworth Sleepiness Scale and STOP-Bang Questionnaire may be used as a screening tool

PHYSICAL—vitals (hypertension, hypoxia). Obtain weight and height (BMI often >30 kg/m^2). Asterixis and plethora secondary to hypercapnia. Check for low-hanging soft palate, large uvula, enlarged tonsils, retrognathia, micrognathia, ↑ neck circumference (>42 cm [>16.5 in.] for ♂, >39 cm [>15.4 in.] for ♀), and acanthosis nigricans. Perform respiratory and cardiac examination (hypertension and pulmonary hypertension, restrictive lung disease). Inspect for potential causes such as nasopharyngeal carcinoma, hypothyroidism (goiter), acromegaly (course facial structures), and amyloidosis (periorbital infiltrate, shoulder pad sign)

CLINICAL FEATURES (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE OBSTRUCTIVE APNEA?

	LR+	LR–
Symptoms		
Nocturnal choking/ gasping	3.3	0.57
Morning headache	1.5–3.8	0.73–0.93
Reported apnea	1.4	0.47
Excessive daytime sleepiness	1.3–1.4	0.80–0.81
Snoring	1.1–1.5	0.12–0.60
Signs		
Mallampati Class 3 or 4	1.6	0.60–0.68
Pharyngeal narrowing	1.4	0.63
Combination of Findings		
Overall clinical impression	1.7	0.67
STOP-Bang Questionnaire	1.4-1.8	0.20-0.23
Snoring Severity Scale ≥4 and BMI ≥26	1.6	0.07
Sleep Apnea Clinical Score (SACS) >15	5.2	–
Sleep Apnea Clinical Score (SACS) ≤5	0.25	–

APPROACH—obstructive sleep apnea is common (2–14% in community screened patients), and is associated with HTN, HF, diabetes and arrhythmia. Individual signs and symptoms lack diagnostic accuracy and are insufficient to rule in/rule out OSA. Snoring is non-specific but patients with a normal BMI who do not snore are unlikely to have OSA. Multi-item questionnaires (e.g. STOP-Bang Questionnaire) may identify patients at low risk of OSA. The Sleep Apnea Clinical Score requires further validation before use for screening in primary care

JAMA 2013 310:7

INVESTIGATIONS

POLYSOMNOGRAPHY
ABG
PFT

MANAGEMENT

LIFESTYLE CHANGES—sleep hygiene (avoid daytime napping, avoid caffeine, reduce alcohol intake, exercise regularly but not immediately before sleep, maintain regular sleep schedule, ensure comfortable sleep environment without noises or bright light), restrict body position during sleep

TREAT UNDERLYING CAUSE—for patients with obstructive sleep apnea, recommend weight loss (diet, exercise, weight management program; consider referral for bariatric surgery if BMI >40 kg/m^2 or >35 kg/m^2 with serious comorbid disease), avoidance of alcohol/sedatives. CPAP is the gold standard for therapy. Other options include orthodontic devices to hold lower jaw forward and surgical procedures such as tracheostomy, tonsillectomy, nasal surgery, uvulopalatopharyngoplasty; however, therapies other than CPAP are not generalizable. Thus, every effort should be made to treat with CPAP

Can Respir J 2011 18:1

TREATMENT ISSUES

PATIENTS WITH OBSTRUCTIVE SLEEP APNEA AND HF—optimization of HF therapy first, then consider trial of CPAP therapy for 3 months if OSA still persists; CPAP can ↑ ventilation during sleep, ↓ hypoxemia, ↑ sleep quality, and ↑ cardiac function (↓ LV transmural pressure and improves cardiac output)

SPECIFIC ENTITIES

OBESITY HYPOVENTILATION SYNDROME (OHS)—also known as Pickwickian syndrome. Defined by hypoventilation (awake $PaCO_2$ >45 mmHg) in the absence of other causes of hypoventilation. OHS patients have sleep disordered breathing, and most have OSA. BMI is usually >35 kg/m^2. Treatment options include respiratory stimulants, ventilatory support (BiPAP), oxygen therapy, and weight loss

NARCOLEPSY—severe daytime hypersomnolence, cataplexy (loss of postural tone, usually with emotions), sleep paralysis (usually happens after sleep–wake transition), hypnagogic hallucinations (visual or auditory hallucinations during drowsiness)

RESTLESS LEG SYNDROME

- **PATHOPHYSIOLOGY**—associated with iron deficiency, hypoparathyroidism, uremic neuropathy, diabetic neuropathy, rheumatoid arthritis, and fibromyalgia

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—desire to move extremities, associated with paresthesias, dysesthesias, and motor restlessness (floor pacing, leg rubbing). Symptoms tend to be worse at rest, particularly in the evenings and at night. Relieved by activity

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—dopamine agonists (pergolide, pramipexole, or ropinirole), levodopa/carbidopa, gabapentin, clonazepam, and oxycodone if precipitated by pain. A trial of iron therapy is indicated in all patients even in the absence of overt iron deficiency

NEJM 2003 348:21

Respiratory Acidosis: Hypoventilation

DIFFERENTIAL DIAGNOSIS

CNS (respiratory center depression)—brain stem injury (tumor, stroke), sleep apnea, obesity, medications (opioids)

RESPIRATORY

- **UPPER AIRWAY OBSTRUCTION**—epiglottitis, laryngospasm
- **LOWER AIRWAY OBSTRUCTION**—COPD, asthma, sleep apnea
- **DEAD SPACE VENTILATION**—infection, pleural effusion
- **NEUROMUSCULAR**—myasthenia gravis, Guillain–Barré syndrome, myopathy, ALS, hypophosphatemia, hypokalemia
- **CHEST WALL RESTRICTION**—kyphosis, scoliosis, ankylosing spondylitis

PHYSIOLOGIC COMPENSATION—secondary to metabolic alkalosis

PATHOPHYSIOLOGY

DEFINITION OF RESPIRATORY ACIDOSIS—$PaCO_2 > 40$ mmHg (or upper limit of normal), which is synonymous with hypoventilation

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, CK
- **IMAGING**—CXR
- **ABG**

MANAGEMENT

ACUTE—ABC, O_2, IV, BIPAP, intubation

TREAT UNDERLYING CAUSE

RELATED TOPICS
Approach to ABG (p. 88)
Metabolic Acidosis (p. 87)
Metabolic Alkalosis (p. 89)

Respiratory Alkalosis: Hyperventilation

DIFFERENTIAL DIAGNOSIS

CARDIOPULMONARY—hypoxia, pneumonia, early restrictive disease, mild HF, pulmonary embolism, mechanical ventilation

NON-CARDIOPULMONARY—fever, sepsis, CNS, anxiety, hyperthyroidism, drugs, pregnancy, liver failure

PHYSIOLOGIC COMPENSATION—secondary to metabolic acidosis

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, TSH, urinalysis, βhCG in women of reproductive age
- **IMAGING**—CXR, CT chest
- **ABG**

SPECIAL

- **SEPTIC WORKUP**—blood C&S, urine C&S
- **D-DIMER**—if suspect PE but low probability

PATHOPHYSIOLOGY

DEFINITION OF RESPIRATORY ALKALOSIS—$PaCO_2 < 40$ mmHg (or lower limit of normal), which is synonymous with hyperventilation

MANAGEMENT

ACUTE—ABC, O_2, IV, sedation (use with great caution as patients may experience respiratory decompensation)

TREAT UNDERLYING CAUSE

Hypoxemia

See HYPOXEMIA (p. 102)

Ventilation Issues

See VENTILATION ISSUES (p. 105)

Approach to Chest Imaging

APPROACH TO CHEST X-RAY INTEPRETATION

1. **ID**—note patient's name, date/time, technique (PA + lateral, or AP); if not stated, assume PA + lateral by default
2. **QUALITY OF CXR**
   - **ROTATION**—equi-distance between clavicular heads and spinous process
   - **PENETRATION**—intervertebral space seen behind cardiac silhouette
   - **INSPIRATION**—at least 6–8 ribs anteriorly, or 9–11 ribs posteriorly
   - **FIELD**—ensure the entire thorax is captured on film
3. **DEVICES**—previous sternotomy, mechanical valves, pacemaker, central lines (tip at level of carina), PICC line, Swan Ganz, endotracheal tube (two vertebral spaces above carina or aortic notch), NG tube, ECG leads, pacer wires, O_2 tubing, nipple markers (used to differentiate nipple shadows from pulmonary nodules)
4. **MSK**
   - **SOFT TISSUES**—fat, muscle, breast shadow
   - **BONES**—rib or clavicular fractures, osteoporosis
5. **MEDIASTINUM WIDENING**—right paratracheal stripe >4 mm, azygous region >4 mm, hilar involvement, AP window, tracheal deviation, carina angle widening
6. **HEART**
   - **CARDIOTHORACIC RATIO**—heart to thorax ratio of >30% on PA film or >50% on AP suggests cardiomegaly
   - **CHAMBER ENLARGEMENT**—see table below
7. **LUNGS**
   - **DIAPHRAGM**—right diaphragm is usually higher on lateral, left diaphragm touches heart border
   - **COSTOPHRENIC ANGLE**—blunting suggests effusion
   - **PLEURA**—convex lesion, thickening, calcifications, pneumothorax (veil-like pleural margin over lung edge with no lung markings extending beyond darker zone)
   - **PARENCHYMA CONSOLIDATION SIGNS**—fluffy density, air bronchograms, silhouette signs (right heart border = RML, left heart border = lingula, right diaphragm = RLL, left diaphragm = LLL)
   - **PARENCHYMA RETICULAR NODULAR PATTERN**
8. **BLIND SPOTS**—behind heart, below diaphragm, spine, paraspinal lines, lung apices, peripheral bones

CHAMBER ENLARGEMENT

	PA film	Lateral film
Left ventricular hypertrophy	Enlargement of left heart border inferiorly and laterally	Enlargement of inferior and posterior aspects of heart (start where left diaphragm intersects IVC, go up 2 cm [0.8 in.] and then posteriorly 1.8 cm [0.7 in.], LVH is likely if still in heart shadow)
Left atrial enlargement	Prominence of left atrial appendage	Enlargement of posterior border of heart
Right atrial enlargement	Bulging right heart border	Enlargement of anterior and superior aspects of heart
Right ventricular hypertrophy	Enlargement of left heart border laterally	Enlargement of anterior and superior aspects of heart

LUNG CAVITIES

INFECTIONS—**bacterial** (*Staphylococcus*, β-hemolytic *Streptococcus*, *Klebsiella*, Enterobacteriaceae, Nocardia [multiple cavities], anaerobes), **mycobacteria** (TB, non-TB), **fungal** (histoplasmosis, coccidioidomycosis), **parasites** (echinococcus or hydatid infection), **seeding from another site** (septic emboli from right-sided endocarditis, multiple cavities)

NEOPLASMS—**bronchogenic cancer** (squamous cell), **metastatic seeding** (usually multiple cavities; squamous cell carcinomas such as nasopharynx, esophagus, or cervix; adenocarcinomas such as lung, breast, and GI tract tumors; melanoma)

VASCULAR—**granulomatosis with polyangiitis** (GPA; multiple cavities with airspace disease), **necrotic rheumatoid nodules** (multiple cavities), **pulmonary embolus** (infarction)

FOCAL INFILTRATE

LOBAR PNEUMONIA

LUNG INFARCTION OR HEMORRHAGE

NEOPLASM (less likely)—bronchoalveolar carcinoma is commonly mistaken as pneumonia initially, with radiographic appearance of focal consolidation in 30%, lymphoma

DIFFUSE AIRSPACE DISEASE

PULMONARY EDEMA (fluid)—**cardiogenic** (left ventricular failure, valvular disease), **non-cardiogenic** (toxic inhalation, drug reaction, aspiration, fat embolism, ARDS)

INFECTIONS (pus)—bacterial, viral, atypical (TB), fungal

HEMORRHAGE (blood)—**bleeding diathesis**, **DIC**, **anticoagulation**, **vasculitis** (GPA, Goodpasture's, SLE)

INFLAMMATORY—cryptogenic organizing pneumonia, eosinophilic pneumonia, pulmonary alveolar proteinosis

MALIGNANCY—bronchoalveolar carcinoma, lymphoma

RETICULAR PATTERN

PULMONARY EDEMA

INFECTIONS—bacterial, viral, PJP

INTERSTITIAL LUNG DISEASE—idiopathic pulmonary fibrosis, drug-induced fibrosis, pneumoconiosis, hypersensitivity pneumonitis, connective tissue disease-related fibrosis, asbestosis, ankylosing spondylitis, sarcoidosis, ABPA, opportunistic infections

RETICULAR PATTERN (CONT'D)

TUMOR—lymphangitic carcinomatosis (subacute)

NODULAR OR RETICULONODULAR PATTERN

INFECTIONS—TB (miliary), viral, fungal

INFLAMMATORY GRANULOMAS—sarcoidosis, silicosis, histiocytosis X, hypersensitivity pneumonitis

METASTASES—melanoma, lung cancer, breast cancer, renal cell carcinoma, germ cell tumors (in young men), thyroid

PLEURAL-BASED DISEASE

THICKENING (obtuse angle, linear)—tumor, edema/post-radiation thickening, fibrosis, consolidation

CALCIFICATIONS—asbestos, TB, empyema, hemothorax

HILAR ENLARGEMENT

LARGE PULMONARY ARTERIES—see PULMONARY HYPERTENSION (p. 65)

BILATERAL HILAR ADENOPATHY—**neoplasm** (lymphoma, metastases), **infections** (viral, TB, fungal), **nonspecific inflammation** (sarcoidosis, silicosis, Berylliosis, connective tissue disease)

LUNG MASS ABUTTING THE HILUM

MEDIASTINAL MASSES

SUPERIOR MEDIASTINUM (above horizontal line drawn between sternomanubrial joint and T4 vertebra)—thyroid goiters, cystic hygromas, adenopathy, aneurysm

ANTERIOR MEDIASTINUM (in front of heart border)

★5 T's★

- **T**hymoma
- **T**hyroid (retrosternal)
- **T**eratoma
- **T**errible lymphoma
- **T**umor—bronchogenic carcinoma

MIDDLE MEDIASTINUM (between anterior heart border and vertebral bodies)—**infections** (TB, fungal), **neoplastic** (bronchogenic, lymphoma, metastases, neurogenic, mesothelioma), **sarcoidosis**, **aneurysm**, **cysts** (bronchogenic, pericardial, esophageal), **Castleman's disease** (giant LN hyperplasia)

POSTERIOR MEDIASTINUM—**neural tumors** (sheath tumors [schwannomas, neurofibromas], ganglion cell tumors [neuroblastoma, ganglioneuroma]), **non-neural tumors** (mesenchymal, vertebral, lymphoma), **Bochdalek's hernia**

SIGNS FOR DISEASE PROCESSES

HEART FAILURE—vascular redistribution/bat wings, cardiomegaly, peribronchial cuffing, Kerley B lines, pulmonary edema, pleural effusion

COPD—hyperinflation, hemidiaphragm height <1 cm on lateral film, large retrosternal airspace, peripheral vessels end bluntly

CYSTIC FIBROSIS—**hyperinflation** (flattened diaphragms, large retrosternal airspace), prominent **interstitial markings** (upper lobes progressing to the lower lobes), **bronchiectasis** (peribronchial cuffing, "tram tracks," ring shadows), **cysts**, **scarring** (retraction of hilar regions), **pulmonary arterial hypertension** (pulmonary arteries dilatation), **pneumothorax**

CT CHEST PROTOCOLS

HIGH RESOLUTION—1 mm cut every 1 cm (10% of chest only). Non-contrast. Best for interstitial lung disease

LUNG CANCER PROTOCOL—7–10 mm cut of entire chest. Also scans adrenals and liver. Contrast enhanced. Best for nodules and mediastinal and pleural structures

PULMONARY EMBOLISM PROTOCOL—contrast bolus timed for optimal imaging of pulmonary arteries. Best for vascular structures, reasonable for nodules and mediastinal and pleural structures

RELATED TOPICS
Interstitial Lung Disease (p. 18)
Solitary Pulmonary Nodule (p. 16)

Approach to Pulmonary Function Tests

OVERALL APPROACH TO PFT INTERPRETATION

1. **ID AND DEMOGRAPHICS**—name, date/time, age, height, weight, BMI, smoking history
2. **ANALYZE FLOW VOLUME LOOP AND SPIROMETRY**—identify obstructive or restrictive pattern
3. **ANALYZE SPIROMETRY**—identify obstructive defect, reversibility, and severity. Note that restrictive defect cannot be diagnosed without knowledge of lung volumes
4. **ANALYZE LUNG VOLUMES**—identify restrictive defect, severity
5. **ANALYZE DLCO AND DLCO ADJUSTED FOR ALVEOLAR VOLUME (VA)**—a measure of gas exchange; if abnormal, suggests disease even if spirometry and lung volumes are normal

CLASSIFICATION OF PULMONARY DISEASES

OBSTRUCTIVE—asthma, COPD, bronchiectasis, cystic fibrosis, bronchiolitis obliterans

RESTRICTIVE

PARENCHYMAL—sarcoidosis, idiopathic pulmonary fibrosis, pneumoconiosis, other interstitial lung diseases

EXTRAPARENCHYMAL—neuromuscular (diaphragmatic paralysis, myasthenia gravis, Guillain–Barré syndrome, muscular dystrophies), chest wall (kyphoscoliosis, obesity, ankylosing spondylitis)

TERMINOLOGIES

DLCO—carbon monoxide diffusion capacity

FEF25–75%—forced expiratory flow during the middle of an FVC maneuver, represents flow of small airways

TERMINOLOGIES (CONT'D)

FEV1—forced expiratory volume during the first second of an FVC maneuver

FVC—forced vital capacity, maximum volume exhaled after maximum inhalation

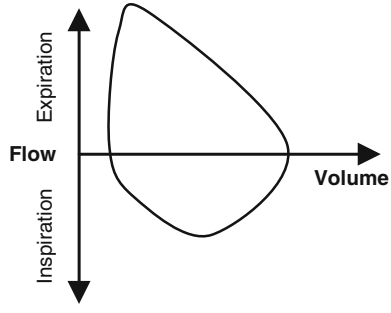
MEP—maximum expiratory pressure

MIP—maximum inspiratory pressure

TLC—total lung capacity at maximal inhalation

FLOW–VOLUME LOOP PATTERNS

NORMAL



OBSTRUCTIVE DISEASE—scooped appearance of expiratory curve seen in COPD. Variable extrathoracic obstruction (e.g. paralyzed vocal cords) appears as flattening of inspiratory curve. Variable intrathoracic obstruction (e.g. tracheal tumor)

FLOW–VOLUME LOOP PATTERNS (CONT'D)

appears as flattening of expiratory curve. Flattening of the inspiratory curve (i.e. negative portion of the flow–volume loop) represents extrathoracic obstruction; intrathoracic obstruction affects the expiratory curve (i.e. positive portion of the flow–volume loop)

RESTRICTIVE DISEASE—expiratory portion of curve appears relatively tall (preserved flow rates), but narrow (↓ lung volumes)

SPIROMETRY AND LUNG VOLUME PATTERNS

OBSTRUCTIVE DISEASE—↓ FEV1/FVC ratio (↓ FEV1 out of proportion to ↓ FVC); definitions vary but GOLD criteria define ↓ FEV1/FVC as <70%. If improvement >12% and 200 mL post-bronchodilator, consider diagnosis of asthma (reversibility). Note that mild obstructive (small airways) disease may have normal FEV1/FVC with ↓ FEF 25–75%

RESTRICTIVE DISEASE—↓ TLC, defined as <80% predicted (only applies to plethysmography); 70–79% = mild; 60–69% = moderate; <60% = severe. Note that patients may have both obstructive and restrictive disease

Note: general rule for the lower limit of normal for most PFT results is 80% of predicted (FEV1, FVC, DLCO, TLC) but less accurate for FEV1/FVC ratio and for patients of extremes of age

SPIROMETRY AND LUNG VOLUME PATTERNS (CONT'D)

OVERALL APPROACH

	TLC	FEV1/FVC	MIP	MEP
Obstructive	N/↑	↓	N	N
Restrictive				
Parenchymal	↓	N/↑	N	N
Extraparenchymal (inspiratory)	↓	N	N/↓	N
Extraparenchymal (inspiratory + expiratory)	↓	↓/N/↑	N/↓	N/↓

ANALYZING DLCO

REFERENCE VALUES FOR DLCO

	% predicted
High	>140%
Normal	81–140%
Borderline low	76–80%
Mild decrease	61–75%
Moderate decrease	41–60%
Severe decrease	<40%

OBSTRUCTIVE DISEASE PRESENT—DLCO usually normal in asthma and chronic bronchitis but ↓ in emphysema

ANALYZING DLCO (CONT'D)

RESTRICTIVE DISEASE PRESENT—DLCO adjusted for alveolar volume usually ↓ in interstitial lung diseases and atelectasis and normal in neuromuscular diseases, chest wall abnormalities, and obesity

ISOLATED DLCO ABNORMALITY (WITHOUT OBVIOUS OBSTRUCTIVE OR RESTRICTIVE DISEASE)—↓ DLCO may result from anemia, ↑ carboxyhemoglobinemia, PE, and pulmonary hypertension; ↑ DLCO may result from pulmonary hemorrhage, obesity, left-to-right shunts, and polycythemia

2
CARDIOLOGY

Bryan Jonathan Har

Aortic Dissection

DIFFERENTIAL DIAGNOSIS

CARDIAC

- **MYOCARDIAL**—myocardial infarction, angina, myocarditis
- **VALVULAR**—aortic stenosis, aortic regurgitation
- **PERICARDIAL**—pericarditis
- **VASCULAR**—aortic dissection

RESPIRATORY

- **PARENCHYMAL**—pneumonia, cancer
- **PLEURAL**—pneumothorax, pneumomediastinum, pleural effusion, pleuritis
- **VASCULAR**—pulmonary embolism, pulmonary hypertension

GI—esophagitis, esophageal cancer, GERD, peptic ulcer disease, Boerhaave's, cholecystitis, pancreatitis

OTHERS—musculoskeletal, shingles, anxiety

PATHOPHYSIOLOGY

ANATOMY—layers of aorta include intima, media, and adventitia. Majority of tears found in ascending aorta at right lateral wall where the greatest shear force is produced

AORTIC TEAR AND EXTENSION—aortic tear may produce a tearing, ripping sudden chest pain radiating to the back. Aortic regurgitation can produce diastolic murmur. Pericardial tamponade may occur, leading to hypotension or syncope. Initial aortic tear and subsequent extension of a false lumen along the aorta may also occlude blood flow into any of the following vascular structures:

- **CORONARY**—acute myocardial infarction (usually RCA)
- **BRACHIOCEPHALIC**, **LEFT SUBCLAVIAN**, **DISTAL AORTA**—absent or asymmetric peripheral pulse, limb ischemia
- **RENAL**—anuria, renal failure
- **CAROTID**—syncope/hemiplegia/death
- **ANTERIOR SPINAL**—paraplegia/quadriplegia, anterior cord syndrome

PATHOPHYSIOLOGY (CONT'D)

CLASSIFICATION SYSTEMS

- **STANFORD**—**A** = any ascending aorta involvement, **B** = all others
- **DEBAKEY**—**I** = ascending and at least aortic arch, **II** = ascending only, **III** = originates in descending and extends proximally or distally

RISK FACTORS

- **COMMON**—hypertension, age, male
- **VASCULITIS**—Takayasu arteritis, giant cell arteritis, rheumatoid arthritis, syphilitic aortitis
- **COLLAGEN DISORDERS**—Marfan syndrome, Ehlers–Danlos syndrome, cystic medial necrosis
- **VALVULAR**—bicuspid aortic valve, aortic coarctation, Turner syndrome, aortic valve replacement
- **OTHERS**—cocaine, trauma

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE AN ACUTE THORACIC AORTIC DISSECTION?

	LR+	LR–
History		
Hypertension	1.6	0.5
Sudden chest pain	1.6	0.3
Tearing or ripping pain	1.2–10.8	0.4–0.99
Physical		
Pulse deficit	5.7	0.7
Focal neurological deficit	6.6–33	0.71–0.87
Diastolic murmur	1.4	0.9
CXR/ECG		
Enlarged aorta or wide mediastinum	2.0	0.3
LVH on ECG	0.2–3.2	0.84–1.2

APPROACH—"presence of tearing, ripping, or migrating pain may suggest dissection. Pulse deficit or focal neurological deficits greatly increase likelihood of dissection. Absence of pain of sudden onset decreases likelihood of dissection. Normal aorta and mediastinum on CXR help to exclude diagnosis"

JAMA 2002 287:17

D. Hui et al. (eds.), *Approach to Internal Medicine: A Resource Book for Clinical Practice*,
DOI 10.1007/978-3-319-11821-5_2, © Springer International Publishing Switzerland 2016

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, troponin/CK × 3, glucose, AST, ALT, ALP, bilirubin, albumin, lipase, INR/PTT
- **IMAGING**—CXR, echocardiogram (TEE), CT chest or MRI chest
- **ECG**

SPECIAL

- **AORTOGRAPHY**

DIAGNOSTIC AND PROGNOSTIC ISSUES

CXR FINDINGS—wide mediastinum (>6 cm [2.4 in.]), indistinct aortic knuckle, pleural cap, difference in diameter between ascending and descending aorta, blurring of aortic margin secondary to local extravasation of blood, pleural effusion or massive hemothorax, displaced calcification (separation of the intimal aortic calcification from the edge of the aortic shadow >1 cm [0.4. in.])

PROGNOSIS

- **TYPE A**—with surgery, 1-month survival 75–80%, 10-year survival 55%

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

- **TYPE B**—with aggressive hypertensive treatment, 1-month survival >90%, 10-year survival 56%

MANAGEMENT

ABC—O_2 to keep sat >95%, IV, **antihypertensive therapy** (keep HR <60 and SBP <120 mmHg. *Labetalol* 2 mg/min IV loading drip, then 2–8 mg/min (target heart rate 55–60) or 20–80 mg IV q10 min, maximum 300 mg, then 200–400 mg PO BID. If SBP still >120 mmHg, *sodium nitroprusside* 0.25–0.5 μg/kg/min IV initially, then 0.25–3 μg/kg/min, maximum 10 μg/kg/min)

TREAT UNDERLYING CAUSE—**Type A** (emergent surgical repair, endovascular stenting, long-term blood pressure control). **Type B** (medical blood pressure control). Monitor over time with serial CT/MR chest

Related Topics
Acute Coronary Syndrome (p. 28)
Stroke (p. 337)

Acute Coronary Syndrome

ACCF/AHA 2013 STEMI Guidelines
ACCF/AHA 2007 UA/NSTEMI Guidelines
ACCF/AHA UA/NSTEMI 2012 Focused Update

DIFFERENTIAL DIAGNOSIS OF CHEST PAIN

CARDIAC

- **MYOCARDIAL**—myocardial infarction, angina (atherosclerosis, vasospasm), myocarditis
- **VALVULAR**—aortic stenosis
- **PERICARDIAL**—pericarditis
- **VASCULAR**—aortic dissection

RESPIRATORY

- **PARENCHYMAL**—pneumonia, cancer

DIFFERENTIAL DIAGNOSIS OF CHEST PAIN (CONT'D)

- **PLEURAL**—pneumothorax, pneumomediastinum, pleural effusion, pleuritis
- **VASCULAR**—pulmonary embolism

GI—esophagitis, esophageal cancer, GERD, peptic ulcer disease, Boerhaave's, cholecystitis, pancreatitis

OTHERS—musculoskeletal (costochondritis), shingles, anxiety

PATHOPHYSIOLOGY

	Pathologic changes	Clinical presentation
Pre-clinical	Atherosclerosis	Asymptomatic
Angina	Luminal narrowing	Central chest discomfort; worsened by exertion, emotion, and eating; relieved by rest and nitroglycerine
Unstable angina	Plaque rupture or thrombus	Worsening pattern or rest pain; no elevation in troponin, with or without ECG changes of ischemia
NSTEMI	Partial occlusion	Non-ST elevation MI; elevation in troponin, with or without ECG changes of ischemia
STEMI	Complete occlusion	ST elevation MI; elevation in troponin, with distinct ST segment elevation in ≥2 contiguous leads, new LBBB, or posterior wall MI with reciprocal ST depression in precordial leads on ECG

PATHOPHYSIOLOGY (CONT'D)

THIRD UNIVERSAL DEFINITION OF MYOCARDIAL INFARCTION (MI)

- **TYPE 1**—spontaneous MI due to a primary coronary event (atherosclerotic plaque rupture or erosion with acute thromboembolism)
- **TYPE 2**—MI secondary to an ischemic imbalance (supply demand mismatch)
- **TYPE 3**—MI resulting in death when biomarker values are unavailable (sudden unexpected cardiac death before serum biomarkers collected for measurement)
- **TYPE 4**—MI related to PCI (4A) or stent thrombosis (4B)
- **TYPE 5**—MI related to CABG

RISK FACTORS

- **MAJOR**—diabetes, hypertension, dyslipidemia, smoking, family history of premature CAD, advanced age, male gender
- **ASSOCIATED**—obesity, metabolic syndrome, sedentary lifestyle, high-fat diet
- **EMERGING**—lipoprotein abnormalities, inflammation (↑ CRP), chronic infections, chronic kidney disease

POST–MI COMPLICATIONS—arrhythmia (VT/VF, bradycardia), sudden death, papillary muscle rupture/dysfunction, myocardial rupture (ventricular free wall, interventricular septum), ventricular aneurysm, valvular disease (especially acute mitral regurgitation), heart failure/cardiogenic shock, peri-infarction pericarditis, post-cardiac injury pericarditis (Dressler's syndrome)

CLINICAL FEATURES

CHEST PAIN EQUIVALENTS—dyspnea, syncope, fatigue, particularly in patients with diabetic neuropathy who may not experience chest pain

NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION

- **I** = no symptoms with ordinary physical activity
- **II** = mild symptoms with normal activity (walking >2 blocks or 1 flight of stairs)
- **III** = symptoms with minimal exertion
- **IV** = symptoms at rest

CANADIAN CARDIOVASCULAR SOCIETY (CCS) CLASSIFICATION

- **I** = angina with strenuous activity
- **II** = slight limitation, angina with meals/cold/stress
- **III** = marked limitation, angina with walking <1–2 blocks or 1 flight of stairs
- **IV** = unstable angina
  - **IVA** = unstable angina resolves with medical treatment

CLINICAL FEATURES (CONT'D)

  - **IVB** = unstable angina on oral treatment, symptoms improved but angina with minimal provocation
  - **IVC** = unstable angina persists, not manageable on oral treatment or hemodynamically unstable

KILLIP CLASS CLASSIFICATION

- **I** = no evidence of heart failure
- **II** = mild to moderate heart failure (S3, lung rales less than half way up, or jugular venous distension)
- **III** = overt pulmonary edema
- **IV** = cardiogenic shock

RATIONAL CLINICAL EXAMINATION SERIES: IS THIS PATIENT HAVING A MYOCARDIAL INFARCTION?

	LR+
History	
Pain radiation to the shoulder OR both arms	*4.1*
Pain radiation to right arm	*3.8*
Radiation to left arm	2.2
Radiation to both arms	*9.7*
Vomiting	*3.5*
Ex-smoker	*2.5*
Diaphoresis	2.0
Pleuritic chest pain	0.2
Sharp or stabbing chest pain	0.3
Positional chest pain	0.3
Chest pain reproducible by palpation	0.2–0.4
Physical	
Hypotension	3.1
S3	3.2
Pulmonary crackles	2.1
ECG	
New ST elevation ≥1 mm	5.7–53.9
New Q wave	5.3–24.8
Any ST elevation	11.2
New conduction defect	6.3
New ST depression	3.0–5.2
Any Q wave	3.9
Any ST depression	3.2
T wave peaking or inversion ≥1 mm	3.1
New T wave inversion	2.4–2.8
Any conduction defect	2.7
Multivariate Prediction Models	
ACI-TIPI (Acute Cardiac Ischemia Time Insensitive Predictive Instrument)	*3.9–12*
Goldman Protocol	*2.9–3.6*

APPROACH—"radiation of chest pain, diaphoresis, hypotension, and S3 suggest acute MI. Chest pain that is pleuritic, sharp or stabbing, positional or reproduced by palpation decreases likelihood of acute MI. On ECG, any ST ↑, new Q waves, or new conduction Δ make acute MI very likely. Normal ECG is very powerful to rule out MI"

JAMA 1998 280:14

CLINICAL FEATURES (CONT'D)

UPDATE—"after clinical symptoms are used to identify patients with possible ischemia, the ECG and troponin results take precedence in making the diagnosis. The presence of diabetes, HTN, or dyslipidemia should not affect clinician's probability estimate that an episode of chest pain represents an ACI"

The Rational Clinical Examination. McGraw-Hill, 2009

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, troponin/CK × 3 q6-8 h, BNP or NT-pro-BNP, AST, ALT, ALP, bilirubin, INR/PTT, Mg, Ca, PO_4, albumin, lipase, fasting lipid profile, random and fasting glucose, HbA1C
- **IMAGING**—CXR, echocardiogram (first 72 h), MIBI/thallium (>5 days later)
- **ECG**—q8h × 3 or with chest pain
- **STRESS TESTS**—ECG, echocardiogram, MIBI once stable (>48 h post-MI)
- **CORONARY CATHETERIZATION**

DIAGNOSTIC AND PROGNOSTIC ISSUES

RISK STRATIFICATION FOR STABLE CORONARY DISEASE

- **ECG EXERCISE STRESS TEST**
  - **ABSOLUTE CONTRAINDICATIONS**—recent myocardial infarction (<4 days), unstable angina, severe symptomatic LV dysfunction, life-threatening arrhythmia, acute pericarditis, aortic dissection, PE, severe symptomatic aortic stenosis
  - **GOAL**—keep on treadmill until subject reaches 85–90% of age-predicted heart rate (220–age)
  - **ISCHEMIA CRITERIA**— ≥ 1 mm horizontal or down-sloping ST ↓ over multiple leads, or ST ↑ → myocardial ischemia (sens 68%, spc 77%) → proceed to angiogram
  - **INCONCLUSIVE**—premature termination due to chest pain/poor exercise tolerance → proceed to pharmacological stress test
  - **DUKE TREADMILL SCORE**—(exercise time in minutes) − 5 × (maximum ST ↓ in mm) − 4 × (treadmill angina index [0 = none, 1 = non-limiting, 2 = exercise limiting]). **Low risk** ≥ +5 (4-year survival 98–99%), **moderate risk** −10 to +4, **high risk** ≤ −11 (4-year survival 71–79%)
- **DIPYRIDAMOLE/ADENOSINE MIBI**—dipyridamole (Persantine) causes vasodilation. In CAD, the coronary artery is already maximally dilated to compensate, so addition of dipyridamole will not change perfusion to diseased vessel(s) further. This results in a relative perfusion mismatch compared to areas with normal dilatory reaction. Contraindicated in asthma/COPD. Antidote is aminophylline or caffeine
- **DOBUTAMINE ECHOCARDIOGRAPHY**—assesses wall motion abnormalities. Compared to MIBI, echocardiogram is more specific and less sensitive. Contraindicated in severe hypertension and arrhythmias

APPROACH TO DIAGNOSIS OF STABLE CAD—start with history, physical, rest ECG, and CXR. If low probability, do not investigate further. If high probability, proceed with management. If intermediate probability → stress test → cardiac CT, MIBI or stress echo → angiography

DIFFERENTIAL DIAGNOSIS OF TROPONIN ELEVATION

- **CARDIAC**—myocardial infarction, myocarditis, congestive heart failure, pericarditis, vasospasm, tachycardia with supply–demand mismatch, drug/cocaine ingestion, stress (takotsubo) cardiomyopathy
- **PULMONARY**—pulmonary embolism
- **HEPATIC**—liver failure
- **RENAL**—chronic kidney disease
- **NEUROLOGIC**—stroke, intracranial hemorrhage
- **SYSTEMIC**—sepsis, prolonged strenuous exercise

SERUM MARKERS

- **TROPONIN I/T**—rises within 4–6 h, peaks at 18–24 h, remains elevated 7–10 days (sens 40% at presentation, 40–70% after 6–9 h of symptoms)
- **CK/CKMB**—rises within 4–6 h, peaks at 18–24 h, remains elevated 3–4 days (sens 35–50% at presentation, 90% after 3 h in ER)
- **MYOGLOBIN**—rises within 1–2 h, peaks in few hours

Therefore, measure markers (e.g., troponin) at least twice separated by 6–8 h with serial ECG. Despite all appropriate investigations, missed MI rate is 2–5%

ECG CHANGES IN ACUTE MI—see APPROACH TO ECG p. 73

TIMI SCORE FOR PATIENTS WITH UNSTABLE ANGINA/NSTEMI

- **SCORING** (out of 7)—age ≥65, ≥3 CAD risk factors, known CAD (stenosis >50%), ASA use within prior 7 days, ≥2 angina episodes within 24 h, ↑ cardiac markers, ST deviation ≥0.5 mm

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

- **RISK GROUPS**—**low** = 0–2, **intermediate** = 3–4, **high** = 5–7. Consider GPIIb/IIIa and early angiography with revascularization in intermediate or high-risk groups
- **RISK OF DEATH, MI OR REVASCULARIZATION IN 14 DAYS**—0/1 = 4.7%, 2 = 8.3%, 3 = 13.2%, 4 = 19.9%, 5 = 26.2%, 6/7 = 40.9%

GRACE RISK SCORE FOR PATIENTS WITH UNSTABLE ANGINA/NSTEMI

- **SCORING** (based on regression model)—age, SBP, HR, creatinine, Killip class, cardiac arrest at admission, presence of ST segment deviation, elevation in serum cardiac enzymes/markers. Risk score calculated using online software: www.outcomes-umassmed.org/grace/acs_risk/acs_risk_content.html

Risk category	GRACE risk score	In-hospital death (%)
Low	≤108	<1
Intermediate	109–140	1–3
High	>140	>3

Risk category	GRACE risk score	6-month death
Low	≤88	<3
Intermediate	89–118	3–8
High	>118	>8

TIMI SCORE FOR PATIENTS WITH STEMI

- **SCORING** (out of 14)—age (3 points = ≥75, 2 points = 65–74), any of diabetes, hypertension, or angina (1 point), systolic BP ≤100 mmHg (3 points), HR >100 (2 points), Killip class II–IV (2 points), weight <67 kg (1 point), anterior ST elevation or LBBB (1 point), time to reperfusion >4 h (1 point)
- **RISK OF DEATH IN 30 DAYS**—0 = 0.8%, 1 = 1.6%, 2 = 2.2%, 3 = 4.4%, 4 = 7.3%, 5 = 12.4%, 6 = 16.1%, 7 = 23.4%, 8 = 26.8%, >8 = 35.9%

IN-HOSPITAL OUTCOMES

	NSTEMI (%)	STEMI (%)
Death	4	6
Reinfarction	0.9	1.1
Cardiogenic shock	2.8	6.4
Stroke	0.7	0.8
Major bleeding	10	12

ACTION registry 2008/2009 data

ACUTE MANAGEMENT

ABC—O_2 to keep sat >95%, IVs, inotropes, consider balloon pump if hemodynamically unstable

PAIN CONTROL—**nitroglycerin** (*nitro drip* 25 mg in 250 mL D5W, start at 5 μg/min IV, then ↑ by 5–10 μg/min every 3–5 min to 20 μg/min, then ↑ by 10 μg/min every 3–5 min up to 200 μg/min, or until relief of pain, stop titration if SBP is <100 mmHg. *Nitro patch* 0.4 mg/h daily. *Nitro spray* 0.4 mg SL q5min × 3. Beware if suspect right ventricular infarction or if patients on sildenafil). ***Morphine*** 2–4 mg IV every 5–15 min PRN

CLOT CONTROL

- **ANTIPLATELET**—***ASA*** 162–325 mg PO chew × 1 dose, then 75–100 mg PO daily indefinitely. $P2Y_{12}$ receptor blockade with ***clopidogrel*** 300–600 mg × 1 dose then 75 mg PO daily for 1 year; or ***ticagrelor*** 180 mg × 1 dose, then 90 mg PO BID for 1 year; or ***prasugrel*** (with PCI only; do not give if history of CVA or TIA, or age ≥75 years) 60 mg × 1 dose then 10 mg daily for 1 year. Combination ASA plus clopidogrel for minimum of 1 month (ideally 1 year)-post PCI with bare-metal stent, or minimum 12 months (possibly indefinitely) for drug-eluting stents. Consider **GPIIb/IIIa inhibitor** if intermediate/high-risk NSTEMI, treated with PCI, and pain unresponsive to nitroglycerin (*tirofiban* 0.4 μg/kg/min × 30 min IV, then continue 0.1 μg/kg/min × 18–24 h; *eptifibatide* 180 μg/kg IV bolus, then 2 μg/kg/min × 18–24 h; or, *abciximab* 0.25 mg/kg IV bolus, then 0.125 μg/kg/min × 12 h)
- **ANTICOAGULATION**—options include **LMWH** (*enoxaparin* 30 mg IV bolus, then 1 mg/kg SC BID for STEMI [no IV bolus for NSTEMI], caution if renal failure or age >75) or **unfractionated heparin** (*unfractionated heparin* 70 U/kg [up to 4,000 U] IV bolus, then 18 U/kg/h [up to 1,000 U/h] and adjust to 1.5–2.5× normal PTT for 72 h). **Factor Xa inhibitors** (*fondaparinux* 2.5 mg SC daily until discharge or 8 days, caution if renal failure). **Direct thrombin inhibitors** (*bivalirudin* 0.1 mg/kg IV bolus then 0.25 mg/kg/h initially, followed by second 0.5 mg/kg bolus before PCI and 1.75 mg/kg/h during PCI, then continue infusion for up to 4 h post-PCI, if needed)
- **REPERFUSION THERAPY**—see **PCI** for details. **Fibrinolytics** for STEMI (*alteplase* 15 mg IV over 2 min, then 0.75 mg/kg over 30 min [maximum 50 mg], then 0.5 mg/kg over 60 min

ACUTE MANAGEMENT (CONT'D)

[overall maximum 100 mg]; or *tenecteplase* IV bolus over 5 s, weight-based dosing: 30 mg for weight <60 kg, 35 mg for 60–69 kg, 40 mg for 70–79 kg, 45 mg for 80–89 kg, 50 mg for ≥90 kg])

RATE CONTROL—start with *metoprolol tartrate* [immediate release] 25 mg PO q6-12 h. Titrate as tolerated up to maximum dose of *metoprolol tartrate* [immediate release] 100 mg PO q12h or *metoprolol succinate* [extended release] 200 mg PO daily. Alternatively, *carvedilol* 6.25 mg PO BID and titrate as tolerated up to 25 mg PO BID. The goal heart rate is 50–55 with normal activity. If ongoing ischemia or refractory hypertension at the time of presentation, may also consider *metoprolol tartrate* 5 mg IV q5min, up to 3 doses. Avoid if HF, low-output state, presence of prolonged first-degree or high-grade AV block, history of reactive airways disease, or MI precipitated by cocaine use. If β-blocker contraindicated, consider non-dihydropyridine calcium channel blockers (*diltiazem* 30–120 mg PO QID or *verapamil* 80–120 mg PO TID [contraindicated if LV dysfunction])

LIPID CONTROL—high-intensity statin such as *atorvastatin* 80 mg PO daily or *rosuvastatin* 40 mg PO daily

BLOOD PRESSURE SUPPORT—for patients with cardiogenic shock, consider IV fluids, inotropes (dobutamine/dopamine), balloon pump, and early revascularization

OVERALL APPROACH

	Stable angina	Unstable angina or NSTEMI	STEMI
ASA	✓	✓	✓
Nitrates	✓	✓	✓
Morphine	±	✓	✓
β-blockers	✓	✓	✓
ACE inhibitors or ARBs	✓	✓	✓
HMG-CoA inhibitors	✓	✓	✓
Heparin or antithrombin	NO	✓	✓
$P2Y_{12}$ inhibitors	NO	✓	✓
GPIIb/IIIa inhibitors	NO	✓ (consider)	NO
Fibrinolytics or PCI[a]	NO	NO	✓
Cardiology consult	Outpatient[b]	CCU[c]	CCU[c]

[a]If initial presentation is to a PCI-capable hospital, then primary PCI should be performed within 90 min from time of first medical contact (FMC). If initial presentation is to a non-PCI-capable hospital, then arrange urgent transfer to PCI-capable hospital if primary PCI can be performed within 120 min from time of FMC. If timely PCI cannot be provided, administer fibrinolytic within 30 min of FMC. Urgent CABG is also an option post-catheterization

[b]Outpatient cardiology for stress test

[c]CCU consult for risk stratification, monitoring, PCI, and/or CABG

ACUTE MANAGEMENT (CONT'D)

CAUTIONS IN TREATMENT OF ACUTE MYOCARDIAL INFARCTION—avoid negative inotropic agents such as β-blockers and non-dihydropyridine calcium channel blockers if clinical heart failure. Avoid administration of nitroglycerin, morphine, and diuretics to patients with right ventricular infarction as these medications can cause venodilation and decrease preload, leading to hypotension

LONG-TERM MANAGEMENT OF CORONARY ARTERY DISEASE

ANTIANGINAL—nitroglycerin (*nitro patch* 0.4–0.8 mg/h daily; nitro spray 0.4 mg SL q5 min × 3; *isosorbide mononitrate* 30 mg PO daily, maximum 240 mg), **β-blocker** (*metoprolol tartrate* [immediate release] 25–100 mg PO BID, *metoprolol succinate* [extended release] *50–200 mg PO daily*, carvedilol 6.25–25 mg PO BID, *bisoprolol* 5–10 mg PO daily), **calcium channel blocker** (*amlodipine* 5–10 mg PO daily)

LONG-TERM MANAGEMENT OF CORONARY ARTERY DISEASE (CONT'D)

ACE INHIBITOR—*ramipril* 2.5–10 mg PO BID, lisinopril 2.5–10 mg PO daily, trandolapril 0.5–4 mg PO daily, perindopril 2–8 mg PO daily. If ACE inhibitor not tolerated, use ARB

ANTIPLATELET—***ECASA*** 81 mg PO daily indefinitely. P2Y12 receptor blockade (***clopidogrel*** 75 mg PO daily; ***ticagrelor*** 90 mg PO BID, or ***prasugrel*** 10 mg PO daily) generally for 1 year after ACS. Combination ASA plus clopidogrel for minimum of 1 month (ideally 1 year)-post PCI with bare-metal stent, or minimum 12 months (possibly indefinitely) for drug-eluting stents. Consider ticagrelor or prasugrel if received PCI

ANTICOAGULATION—controversial especially in combination with ASA and/or $P2Y_{12}$ inhibitor. May be considered for patients post-STEMI or NSTEMI with one of the following criteria: (1) atrial fibrillation, (2) left ventricular thrombus, (3) significant left ventricular dysfunction with extensive regional wall motion abnormalities. Start *warfarin* 5 mg daily within 72 h and continue heparin/LMWH until INR is between 2 and 3 (unless planning angioplasty). Beware bleeding risk. If possible, minimize duration of "triple therapy" (i.e., ASA, $P2Y_{12}$ inhibitor, and warfarin), consider GI protection with proton-pump inhibitor, and target lower INR (e.g., 2.0-2.5)

RISK REDUCTION ★ABCDEFG★

- **ASA/ACE INHIBITOR/ARB**
- **BLOOD PRESSURE CONTROL** (see HYPERTENSION p. 65)
- **CHOLESTEROL CONTROL** (see DYSLIPIDEMIA p. 70)
- **DIABETIC CONTROL** (see DIABETES p. 381)
- **EXERCISE** (30 min of moderate-intensity exercise 3–4×/week)
- **FAT REDUCTION** (see OBESITY ISSUES p. 457)
- **GET GOING TO QUIT SMOKING!** (see SMOKING ISSUES p. 480)

DRIVING POST-MYOCARDIAL INFARCTION—see p. 490 for details

TREATMENT ISSUES

RIGHT VENTRICULAR INFARCTION—evidence of inferior MI should automatically trigger one to check right-sided leads (V4R) to assess for the possibility of RV infarction, which occurs in about 50% of patients with inferior MI. May see increased JVP, Kussmaul sign, and clear lungs clinically. ST elevation in V4R is diagnostic and prognostic. Hypotension should be treated with fluid bolus to ensure good preload

TREATMENT ISSUES (CONT'D)

POSTERIOR INFARCTION—ST depression in V1–V2 in a regular ECG should automatically trigger one to request for posterior (V7–V9) leads to check for posterior MI. Posterior infarct may be associated with inferior infarcts (90%) and lateral infarcts (10%) as the PDA may be supplied by the right or left circumflex coronary artery

POST-MI RISK STRATIFICATION

- **EXTENT OF INFARCT/RESIDUAL FUNCTION**—assessment is based on clinical factors (↑ HR, ↓ BP, Killip class, diabetes, renal failure, ↑ WBC, GRACE risk score, TIMI risk score), ECG, biomarkers (CK, troponin), imaging (echocardiogram, MIBI, cardiac MRI), and angiography. Early measurement of LV function, although of prognostic importance, is misleading as myocardium function may improve in first 2 weeks. Medical management according to risk
- **EXTENT OF MYOCARDIUM AT RISK**—assessment is based on exercise stress test, stress echocardiogram, stress sestamibi (ischemic tissue), thallium scan (viable tissue), PET scan, cardiac MRI, angiography. Angioplasty or CABG should be considered
- **RISK OF ARRHYTHMIA**—high risk of VF/VT within the first 48 h, therefore monitor with telemetry. If it occurs after 48 h, consider antiarrhythmics and early ICD

BALLOON PUMP—a long balloon in the descending aorta that deflates during systole and inflates during diastole to augment coronary perfusion and cardiac output as well as decrease afterload. Reasonable for severe refractory ischemia and hemodynamic instability. May be used in conjunction with inotropes. Contraindicated in aortic regurgitation, AAA, aortic dissection, uncontrolled sepsis bleeding disorder, and severe PVD

FIBRINOLYTICS USE

- **INDICATIONS**—>120 min anticipated delay from first medical contact to primary PCI, ≥30 min of chest pain, patient presentation within 12 h (ideal door to needle time <30 min), ECG criteria (>1 mm ST ↑ in ≥2 contiguous leads, or new LBBB with suggestive history, age <75)
- **ABSOLUTE CONTRAINDICATIONS**—any intracranial hemorrhage; ischemic stroke within 3 months (except acute ischemic stroke within first 4.5 h); structural cerebral vascular lesion; malignant

TREATMENT ISSUES (CONT'D)

intracranial neoplasm; closed-head or facial trauma within 3 months; intracranial or intra spinal surgery within 2 months); severe uncontrolled hypertension (unresponsive to emergency therapy); suspected aortic dissection; bleeding diathesis or active bleeding (excluding menses)

- **RELATIVE CONTRAINDICATIONS**—chronic, poorly-controlled, severe hypertension; severe hypertension on presentation (>180/110 mmHg); ischemic stroke >3 months; dementia; other intracranial pathology (not already specified above); internal bleeding within 2–4 weeks; active peptic ulcer; major surgery within 3 weeks; non-compressible vascular punctures; use of anticoagulation therapy; pregnancy; traumatic CPR >10 min; prior exposure to streptokinase (if planning to use this fibrinolytic again)
- **RISK OF BLEEDING**—average risk of severe bleed is 1.8%. Increased risk with women, BP >165/95 mmHg, age >65, weight <70 kg [<154 lbs], and lysis with TPA (+0.5% absolute risk/factor)
- **PERSISTENT ST ELEVATION**—look for resolution of symptoms and ST elevation to decrease by >50% within 90 min of fibrinolytic therapy. Persistent ST elevation may suggest failed fibrinolytic therapy, and requires urgent rescue catheterization. Other causes of ST elevation include pericarditis, ventricular aneurysm, hyperkalemia, LBBB, and early repolarization abnormality

Related Topics
Aortic Dissection (p. 27)
Asystole (p. 495)
Diabetes Mellitus (p. 381)
ECG (p. 73)
Hyperlipidemia (p. 70)
Hypertension (p. 65)
Pericarditis (p. 35)
Shock (p. 108)
Smoking Cessation (p. 480)

TREATMENT ISSUES (CONT'D)

PERCUTANEOUS CORONARY INTERVENTION (PCI, PTCA)

- **INDICATIONS FOR ACUTE STEMI**—patient presents within 12 h of chest pain (at a PCI-capable hospital, ideal time from first medical contact to device or "FMC-to-device time" ≤90 min; if at a non-PCI-capable hospital requiring transfer for primary PCI, then ideal "FMC-to-device time" ≤120 min), ECG criteria (>1 mm ST ↑ in ≥2 contiguous leads, new or presumed new left bundle branch block), contraindications to fibrinolysis, or in patients in cardiogenic shock irrespective of time of MI onset
- **INDICATIONS FOR CHRONIC STABLE CAD**—single/double vessel disease refractory to medical therapy. Decision for revascularization (PCI vs. CABG) should follow assessment by heart team (interventional cardiology and cardiac surgery)
- **ADVERSE EVENTS**—access site (bleeding, hematomas, arteriovenous fistulae, pseudoaneurysms), contrast nephropathy, arrhythmia (VT, VF), stroke, dissection, myocardial infarction, death
- **BARE METAL STENTS VS. DRUG-ELUTING STENTS**—in-stent restenosis is due to fibrosis of coronary vasculature and usually happens 3 months post-procedure. Drug-eluting stents (sirolimus, paclitaxel, everolimus, or zotarolimus) are designed to inhibit cell proliferation and decrease the risk of in-stent restenosis. There has been some controversy regarding higher adverse events in patients with first generation drug-eluting stents (sirolimus or paclitaxel). The most recent outcomes research analysis suggests that newer-generation drug-eluting stents (everolimus or zotarolimus) are associated with a decreased rate of repeat revascularization, stent thrombosis, and no significant difference in mortality
- **BENEFITS**—primary PCI is generally preferred given the superior outcomes compared to fibrinolysis, particularly if (1) fibrinolysis contraindicated, (2) previous history of CABG, or (3) cardiogenic shock. However, patients who are able to seek medical attention within 1 h of chest pain onset, have allergy to contrast dye, or do not have access to PCI in a timely fashion should consider fibrinolytics

TREATMENT ISSUES (CONT'D)

OUTCOMES FOR FIBRINOLYTICS VS. PRIMARY PCI

	Fibrinolytics (%)	Primary PCI (%)
Non-fatal reinfarction	7	3
Stroke	2	1
Death (4–6 weeks)	7–9	5–7
Combined endpoint of death–fatal reinfarction and stroke	14	8

NEJM 2007 356:1; NEJM 2007 356:10; NEJM 2007 357:16

CORONARY ARTERY BYPASS GRAFT SURGERY

- **CORONARY ANATOMY**
  - **RIGHT CORONARY** (RCA)—gives rise to right marginal (RMA), right posterior descending (RPDA), and right posterolateral branches (RPL 1, 2, 3)
  - **LEFT MAIN** (LM)—gives rise to left anterior descending (LAD) → diagonal (D1, 2 3) and septals; ramus intermediate (Ram Int); and left circumflex (LCX) → obtuse marginal (OM 1, 2, 3)
  - **DOMINANT ARTERY**—defined as the artery that supplies PDA and at least one posterolateral (PL) artery
- **INDICATIONS**—studies suggest CABG provides mortality benefit for specific subgroups, including patients with (1) left main disease >50% occlusion, (2) two vessel disease with

TREATMENT ISSUES (CONT'D)

significant involvement of proximal left anterior descending, and (3) diffuse triple vessel disease. Diabetic patients and those with reduced left ventricular function derive more benefit from bypass surgery. Angiographic disease severity should be assessed using the SYNTAX score. Decision for revascularization (PCI vs. CABG) should follow assessment by heart team (interventional cardiology and cardiac surgery)

- **MORBIDITY BENEFIT**—95% have improvement of symptoms immediately after surgery, 75% symptom free at 5 years. Recurrent disease more common in vein grafts than artery grafts
- **GRAFTS**—saphenous veins from calf or thigh (SVG), internal mammary arteries (LIMA/RIMA), radial arteries (RA), and gastroepiploic artery from stomach (GA). A total of 90% of arterial graft and 50% of vein graft remain patent by 10 years
- **COMPLICATIONS**
  - **CARDIAC**—MI 2–4%, arrhythmia (AF 40%, sustained VT/VF 2–3%), AV block requiring pacemaker 0.8–4%, pericarditis/tamponade, aortic dissection
  - **NEUROLOGICAL**—stroke, postoperative delirium, cognitive impairment, depression, phrenic nerve damage, intercostal nerve damage
  - **OTHERS**—renal failure, bleeding, infection, pleural effusions, death
- **MEDICATIONS**—hold clopidogrel or ticagrelor 5–7 days prior to CABG. Continue ASA before and after surgery

Pericardial Diseases: Pericarditis and Tamponade

DIFFERENTIAL DIAGNOSIS

★MINT★

METABOLIC—uremia, dialysis, hypothyroidism
MEDICATIONS—procainamide, hydralazine, INH, phenytoin, penicillin
INFARCTION—MI (early, late)
INFECTIOUS—HIV, Coxsackie, echovirus, adenovirus, TB

DIFFERENTIAL DIAGNOSIS (CONT'D)

INFLAMMATORY—psoriatic arthritis, enteric arthritis, rheumatoid arthritis, SLE, mixed connective tissue disease

IDIOPATHIC

NEOPLASTIC—primary (mesothelioma), metastasis (breast, lung, melanoma), leukemia, lymphoma
TRAUMA—stab, gunshot wound, blunt, CPR, postpericardiotomy

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT WITH A PERICARDIAL EFFUSION HAVE CARDIAC TAMPONADE?

	Sens (%)
History	
Dyspnea	87–89
Fever	25
Chest pain	20
Cough	7–10
Physical	
Tachycardia	77
Pulsus paradoxus >10 mmHg[a]	82
Elevated JVP	76
↓ heart sounds	28
Hypotension	26
Hypertension	33
Tachypnea	80
Peripheral edema	21–28
Pericardial rub	19–29
Hepatomegaly	28–55
Kussmaul sign	26
ECG	
Low voltage	42
Atrial arrhythmia	6
Electrical alternans	16–21
ST elevation	18–30
PR depression	18

[a]Pulsus paradoxus LR+ 3.3, LR– 0.03

APPROACH—"among patients with cardiac tamponade, a minority will not have dyspnea, tachycardia, elevated JVP, or cardiomegaly on chest radiograph. A pulsus paradoxus >10 mmHg among patients with a pericardial effusion helps distinguish those with cardiac tamponade from those without. Diagnostic certainty of the presence of tamponade requires additional testing"

JAMA 2007 297:16

DISTINGUISHING FEATURES OF ACUTE TAMPONADE AND CHRONIC CONSTRICTIVE PERICARDITIS

	Acute tamponade	Constrictive pericarditis
Vitals	Tachycardia, hypotension +++, **pulsus paradoxus**	Hypotension, pulsus paradoxus (rare)
JVP	Elevated, Kussmaul (rare) Prominent *x*′ descent but blunted *y* descent	Elevated, **Kussmaul** Prominent *x*′ and *y* descent (Friedrich's sign)
Apex beat	Impalpable	Impalpable
Heart sounds	Distant	Distant, early S3/knock
Other features	Dullness and bronchial breath sounds over left base (Ewart sign)	Hepatosplenomegaly, edema

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, troponin, CK
- **IMAGING**—CXR (calcification if constrictive disease), echocardiogram
- **ECG**—may have sinus tachycardia, low voltages, and electrical alternans in tamponade/effusion; diffuse ST elevation (concave up) and PR depression may be seen in pericarditis

SPECIAL

- **PERICARDIOCENTESIS**—diagnostic or therapeutic (for tamponade, TB/bacterial pericarditis, or large persistent effusion)
- **PERICARDIOSCOPY**
- **CT/MRI CHEST**—if suspect constrictive pericarditis

MANAGEMENT

ACUTE PERICARDITIS—NSAIDs (*indomethacin* 25–50 mg PO TID, *ibuprofen* 600–800 mg PO TID×2–4 weeks, or until resolution of pain) for most cases of idiopathic or viral pericarditis, but avoid after acute MI. If post-MI, ***ASA*** 650 mg PO TID×3–4 weeks. Adjuvant ***colchicine*** 0.6 mg PO BID×3 months in addition to NSAID/ASA to reduce risk of recurrence. ***Prednisone*** 0.25–0.5 mg/kg PO daily×2 weeks (followed by taper) may be considered for connective tissue-mediated disease, although symptoms may recur upon withdrawal

RECURRENT PERICARDITIS—*ASA* 650 mg PO TID×4–8 weeks or **NSAIDs** (*indomethacin* 25–50 mg PO TID, *ibuprofen* 600–800 mg PO TID×4–8 weeks). Add ***colchicine*** (0.6 mg PO BID×3–6 months) for longterm prophylaxis. Avoid anticoagulation as risk of hemopericardium. ***Prednisone*** 0.25–0.5 mg/kg PO daily may also be useful, although symptoms may recur upon withdrawal

MANAGEMENT (CONT'D)

TAMPONADE—ABC, $\mathbf{O_2}$, IV's, bolus IV fluids, **pericardiocentesis** (subxyphoid blind approach, echocardiogram-guided parasternal or apical approach), **pericardiectomy**, **pericardial window** if recurrent/malignant effusion. Avoid nitroglycerin and morphine if tamponade as they may decrease preload, leading to worsening of cardiac output

CONSTRICTIVE PERICARDITIS—complete pericardiectomy

SPECIFIC ENTITIES

ACUTE PERICARDITIS—may be preceded by upper respiratory tract infection. Diagnosis is based on any two of the following inflammatory signs (LR+ 5.4): fever, pericardial friction rub (three components), characteristic chest pain (better with upright position and leaning forward, or pleuritic), PR depression, and diffuse ST elevation. Large effusion without inflammatory signs or tamponade suggests chronic idiopathic pericardial effusion (LR+ 20)

RECURRENT PERICARDITIS—returns in days to weeks upon stopping medications. Likely causes include rheumatologic disorders, Dressler's syndrome, and post-pericardiotomy syndrome

TAMPONADE—a *clinical* diagnosis based on dyspnea, tachycardia, hypotension, pulsus paradoxus, and elevated JVP. Tamponade causes restriction in left or right ventricular diastolic filling. Tamponade with inflammatory signs suggests malignant effusion (LR+ 2.9)

CONSTRICTIVE PERICARDITIS—contraction of pericardium due to chronic inflammation, leading to left and/or right heart failure. May follow pericarditis or radiation. May be difficult to distinguish from restrictive cardiomyopathy clinically

Heart Failure

NEJM 2003 348:20
Canadian Heart Failure Guidelines 2006
Canadian Heart Failure Guidelines Updates 2017–2013

DIFFERENTIAL DIAGNOSIS OF HF EXACERBATION/DYSPNEA

CARDIAC

- **MYOCARDIAL**—HF exacerbation, myocardial infarction
- **VALVULAR**—aortic stenosis, acute aortic regurgitation, mitral regurgitation/stenosis, endocarditis
- **PERICARDIAL**—tamponade
- **DYSRHYTHMIA**

DIFFERENTIAL DIAGNOSIS OF HF EXACERBATION/DYSPNEA (CONT'D)

RESPIRATORY

- **AIRWAY**—COPD exacerbation, asthma exacerbation, acute bronchitis, bronchiectasis, foreign body obstruction
- **PARENCHYMA**—pneumonia, cryptogenic organizing pneumonia, ARDS, interstitial lung disease exacerbation

DIFFERENTIAL DIAGNOSIS OF HF EXACERBATION/DYSPNEA (CONT'D)

- **VASCULAR**—pulmonary embolism, pulmonary hypertension
- **PLEURAL**—pneumothorax, pleural effusion

SYSTEMIC—sepsis, ARDS, metabolic acidosis, anemia, neuromuscular, psychogenic, anxiety

PATHOPHYSIOLOGY

ANATOMIC/PHYSIOLOGIC CLASSIFICATION OF CARDIOMYOPATHY

- **DILATED** (dilatation and impaired contraction of one or both ventricles)—idiopathic, ischemic, valvular, viral, genetic, late manifestation of hypertrophic heart disease, tachycardia induced, alcohol induced, peripartum
- **HYPERTROPHIC** (disorder with disproportionate hypertrophy of the left ventricle and occasionally right ventricle)—**idiopathic** (autosomal dominant inheritance with incomplete penetrance), **storage disease** (Fabry's disease, Pompe disease, Hurler's syndrome, Noonan's syndrome), athlete's heart, obesity, amyloid
- **RESTRICTIVE** (non-dilated ventricles with impaired ventricular filling)—idiopathic familial, **infiltrative** (amyloidosis, hemochromatosis, sarcoidosis), drugs, radiation, endomyocardial fibrosis
- **ARRHYTHMOGENIC RIGHT VENTRICULAR** (replacement of right ventricular free wall with fatty tissue)—arrhythmogenic right ventricular dysplasia
- **UNCLASSIFIABLE**—endocardial fibroelastosis, left ventricular non-compaction

ETIOLOGIC CLASSIFICATION OF CARDIOMYOPATHY

- **ISCHEMIC CARDIOMYOPATHY** (mostly dilated)—varying degrees of persistent ischemia, infarction, and left ventricular remodeling
- **VALVULAR CARDIOMYOPATHY** (mostly dilated)—abnormal loading conditions and secondary left ventricular remodeling and dysfunction
- **HYPERTENSIVE CARDIOMYOPATHY** (dilated, restrictive)—left ventricular hypertrophy and dysfunction
- **DIABETIC CARDIOMYOPATHY** (dilated)—left ventricular dysfunction in the absence of atherosclerosis or hypertension
- **INFLAMMATORY CARDIOMYOPATHY** (mostly dilated)—**infectious** (diphtheria, rheumatic fever, scarlet fever, typhoid fever, meningococcal, TB, Lyme disease, Leptospirosis, RMSF, poliomyelitis, influenza, mumps, rubella, rubeola, variola, varicella, EBV, Coxsackie virus, echovirus, CMV, hepatitis, rabies, mycoplasma, psittacosis, arboviruses, histoplasmosis, cryptococcosis, Chagas disease), **autoimmune**, **idiopathic** myocardial inflammatory diseases

PATHOPHYSIOLOGY (CONT'D)

- **METABOLIC CARDIOMYOPATHY** (dilated, restrictive, and/or hypertrophic)—**endocrine** (thyrotoxicosis, hypothyroidism, acromegaly, pheochromocytoma), **storage diseases** (glycogen storage disease, Fabry's disease, Gaucher's disease, Niemann–Pick disease), **nutritional deficiencies** (Beriberi, Kwashiorkor, pellagra), **deposition** (amyloidosis, hemochromatosis, sarcoidosis)
- **MUSCULAR DYSTROPHIES** (mostly dilated)—Duchenne, Becker's, myotonic dystrophy
- **NEUROMUSCULAR**—Friedreich's ataxia (hypertrophic), Noonan's syndrome, lentiginosis
- **GENERAL SYSTEMIC DISEASE** (mostly dilated)—**connective tissue diseases** (rheumatoid heart disease, ankylosing spondylitis, SLE, scleroderma, dermatomyositis), granulomatous (sarcoidosis, Wegener's granulomatosis, granulomatous myocarditis), **other inflammatory** (giant cell myocarditis, hypersensitivity myocarditis), **neoplasm** (primary, secondary, restrictive pattern)
- **SENSITIVITY AND TOXIC REACTIONS** (mostly dilated)—alcohol, amphetamine, arsenic, catecholamines, cocaine, anthracyclines, zidovudine, radiation (restrictive as well)
- **PERIPARTUM** (dilated)—see p. 471

FUNCTIONAL CLASSIFICATION OF HEART FAILURE

- **SYSTOLIC DYSFUNCTION** (↓ LVEF <45%)—S3 (dilated ventricle with volume overload). Mechanisms include decreased contractility and increased afterload. Causes include MI, cardiomyopathy (dilated, infiltrative), valvular (aortic regurgitation, mitral regurgitation, "burned out" aortic stenosis), "burned out" hypertension and myocarditis
- **DIASTOLIC DYSFUNCTION** (normal LVEF)—S4 (stiff ventricle), LVH, ↓ ventricular relaxation, normal LVEF, ↑ chamber pressures. Mechanisms include decreased active relaxation and passive relaxation (stiff ventricle). Causes include ischemia, hypertension, valvular (aortic stenosis), cardiomyopathy (restrictive, hypertrophic), and pericardial disease
- **MIXED DYSFUNCTION**—in many cases, diastolic dysfunction is present with systolic heart failure

PATHOPHYSIOLOGY (CONT'D)

PRECIPITANTS OF HF ★FAILURE★

- **F**orget to take medications (non-adherence)
- **A**rrhythmia, anemia
- **I**nfection, ischemia, infarction
- **L**ifestyle change

PATHOPHYSIOLOGY (CONT'D)

- **U**pregulators (thyroid, pregnancy)
- **R**heumatic heart disease, acute valvular disease
- **E**mbolism

CLINICAL FEATURES

DISTINGUISHING FEATURES BETWEEN COPD AND HEART FAILURE

	COPD	Heart Failure
History	Previous COPD Medications	Previous HF Medications
Inspect	Nicotine stain, barrel chest Laryngeal height <4 cm	
Cardiac exam	Subxyphoid cardiac pulse	Elevated JVP, S3, S4
Resp. exam	Hyperresonance Prolonged expiratory time	Bilateral crackles
Investigations	CXR shows hypeinflation ABG shows hypercapnia and hypoxemia	CXR shows redistribution and cardiomegaly ABG shows hypoxemia Elevated BNP

CLINICAL FEATURES (CONT'D)

LEFT HEART FAILURE—left-sided S3, rales, wheezes, tachypnea. Causes include previous MI, aortic stenosis, and left-sided endocarditis

RIGHT HEART FAILURE—right-sided S3, ↑ JVP, ascites, hepatomegaly, peripheral edema. Causes include left heart failure, pulmonary hypertension, right ventricular MI, mitral stenosis, and right-sided endocarditis

CLINICAL FEATURES (CONT'D)

GRADING OF PITTING EDEMA—**0** = no edema, **1** = trace edema, **2** = moderate edema disappears in 10–15 s, **3** = stretched skin, deep edema disappears in 1–2 min, **4** = stretched skin, fluid leaking, very deep edema present after 5 min

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS DYSPNEIC PATIENT IN THE EMERGENCY DEPARTMENT HAVE CONGESTIVE HEART FAILURE?

	Sens (%)	Spc (%)	LR+	LR–
History				
Initial clinical judgment	61	80	4.4	0.45
Hx heart failure	60	90	5.8	0.45
Myocardial infarction disease	40	87	3.1	0.69
Coronary artery	52	70	1.8	0.68
Dyslipidemia	23	87	1.7	0.89
Diabetes	28	83	1.7	0.86
Hypertension	60	56	1.4	0.71
Smoker	62	27	0.84	1.4
COPD	34	57	0.81	1.1
PND	41	83	2.6	0.70
Orthopnea	50	77	2.2	0.65
Edema	51	76	2.1	0.64
Dyspnea on exertion	84	34	1.3	0.48
Fatigue and weight gain	31	70	1.0	0.99
Cough	36	61	0.93	1.0

CLINICAL FEATURES (CONT'D)

	Sens (%)	Spc (%)	LR+	LR–
Physical				
S3	13	99	11	0.88
AJR	24	96	6.4	0.79
JVD	39	92	5.1	0.66
Rales	60	78	2.8	0.51
Any murmur	27	90	2.6	0.81
Lower extremity edema	50	78	2.3	0.64
Valsalva maneuver	73	65	2.1	0.41
SBP <100 mmHg	6	97	2.0	0.97
S4	5	97	1.6	0.98
SBP ≥150 mmHg	28	73	1.0	0.99
Wheezing	22	58	0.52	1.3
Ascites	1	97	0.33	1.0
CXR				
Pulmonary venous congestion	54	96	12	0.48
Interstitial edema	34	97	12	0.68
Alveolar edema	6	99	6.0	0.95
Cardiomegaly	74	78	3.3	0.33
Pleural effusions	26	92	3.2	0.81
Any edema	70	77	3.1	0.38
Pneumonia	4	92	0.50	1.0
Hyperinflation	3	92	0.38	1.1
ECG				
Atrial fibrillation	26	93	3.8	0.79
New T wave changes	24	92	3.0	0.83
Any abnormal finding	50	78	2.2	0.64
ST elevation	5	97	1.8	0.98
ST depression	11	94	1.7	0.95
BNP				
BNP ≥ 250 pg/mL			*4.6*	
BNP ≥ 100 pg/mL[a]			*2.7*	
BNP ≥ 50 pg/mL			*1.7*	*0.06*

[a]For patients with an estimated GFR of 15–60 mL/min/1.73 m^2, a threshold of 201 pg/mL can be used

APPROACH—"the features evaluated in more than one study with the highest LRs (>3.5) for diagnosing heart failure were the following: the overall clinical judgment, history of heart failure, S3, jugular venous distension, pulmonary venous congestion or interstitial edema on CXR, and atrial fibrillation on ECG. The features evaluated in more than one study with the lowest LRs (<0.60) for diagnosing of heart failure were the following: the overall clinical judgment, no prior history of heart failure, no dyspnea on exertion, the absence of rales, and the absence of radiographic pulmonary venous congestion, or cardiomegaly. The single finding that decreased the likelihood of heart failure the most was a BNP <100 pg/mL. While the findings of this study are useful when assessing dyspneic patients suspected of having heart failure, no individual feature is sufficiently powerful in isolation to rule heart failure in or out. Therefore, an overall clinical impression based on all available information is best. If the appropriate constellation of findings with high LRs for heart failure are present, that may be sufficient to warrant empirical treatment without further urgent investigations"

JAMA 2005 294:15

The Rational Clinical Examination. McGraw-Hill, 2009

CLINICAL FEATURES (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE ABNORMAL CENTRAL VENOUS PRESSURE?

JVP VS. CAROTID—JVP has biphasic waveforms, is non-palpable, is occludable, decreases with inspiration, changes with position, and increases with abdominojugular reflux (AJR). To perform the AJR, the blood pressure cuff is pumped 6× and then pressed against the abdomen at 20–35 mmHg for 15–30 s. Normal = no change in JVP, or transient increase of >4 cm that returns to baseline before 10 s, or sustained increase <3 cm throughout. Positive AJR occurs when abdominal compression causes a sustained increase in JVP >4 cm (sens 24%, spc 96%, LR+ *4.4*)

JAMA 1996 275:8

UPDATE—a JVP height ≥3 cm above the sternal angle in any position indicates an abnormal CVP. Clinical assessment of high JVP has a LR+ for high CVP of 3.1. An assessment of low JVP has a LR+ for low CVP of 3.4

The Rational Clinical Examination. McGraw-Hill, 2009

RATIONAL CLINICAL EXAMINATION SERIES: CAN THE CLINICAL EXAMINATION DIAGNOSE LEFT-SIDED HEART FAILURE IN ADULTS?

INCREASED FILLING PRESSURE—very helpful findings are **radiographic redistribution** and **jugular venous distension**. Somewhat helpful findings are dyspnea, orthopnea, tachycardia, decreased systolic or pulse pressure, S3, rales, and abdominojugular reflux. Edema is helpful only when present

SYSTOLIC DYSFUNCTION—very helpful findings are **radiograph** (cardiomegaly, redistribution), **anterior Q waves**, **LBBB**, and **abnormal apical impulse** (especially if sustained). Somewhat helpful findings are tachycardia, decreased blood pressure or pulse pressure, S3, rales, dyspnea, previous infarction other than anterior, and high peak CK (post-infarct). Edema and increased jugular venous pressure are helpful if present

DIASTOLIC DYSFUNCTION—very helpful finding is **elevated blood pressure** during the episode of increased filling pressure. Somewhat helpful findings are obesity, lack of tachycardia, older age, and absence of smoking or CAD. Normal radiographic heart size is helpful if present

CLINICAL FEATURES (CONT'D)

APPROACH—"in patients without known systolic dysfunction, ≤1 finding of increased filling pressure can exclude diagnosis, ≥3 findings suggests increased filling pressure. In patients with known systolic dysfunction, absence of finding of increased filling pressure can exclude diagnosis, ≥1 finding suggests increased filling pressure. For systolic dysfunction, can exclude diagnosis if no abnormal findings, including no sign of increased filling pressure are present (LR– 0.1). ≥3 findings are needed to confirm the diagnosis (LR+ 14)"

JAMA 1997 277:21

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, troponin/CK × 3, BNP or NT-pro-BNP, D-dimer, TSH, albumin
- **IMAGING**—CXR, echocardiogram (check E/A ratio if diastolic dysfunction)
- **ECG**

SPECIAL

- **FURTHER IMAGING**—MIBI, MUGA
- **STRESS TEST**—to assess ischemic heart disease
- **CARDIAC CATHETERIZATION**
- **ABG**—if severe dyspnea

DIAGNOSTIC AND PROGNOSTIC ISSUES

B-TYPE NATRIURETIC PEPTIDE/N-TERMINAL PROHORMONE OF BRAIN NATRIURETIC PEPTIDE

- **DIAGNOSIS**—BNP and NT-proBNP levels are elevated with HF, PE, pulmonary hypertension, LVH, ACS, AF, renal failure, overload, and sepsis. Generally, can rule-out HF if BNP <100 pg/mL or NT-proBNP <300 pg/mL; may rule-in if BNP >500 pg/mL, NT-proBNP >900 pg/mL (if age 50–75 years), or NT-proBNP >1,800 pg/mL (if age >75 years). Best used in combination with clinical scoring system when diagnosis is uncertain
- **BAGGISH CLINICAL SCORING SYSTEM**—elevated NT-proBNP [>450 pg/mL if age <50 years, or >900 pg/mL if age ≥50 years] (+4), interstitial edema on CXR (+2), orthopnea (+2), lack of fever (+2), age >75 years (+1), lack of cough (+1), use of loop diuretic prior to presentation (+1), rales (+1). If score 0–5, low likelihood of

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

HF; if 6–8, intermediate likelihood of HF; if 9–14, high likelihood of HF

- **PROGNOSIS**—BNP >80th percentile is associated with a >50% increase in long-term mortality

HF PROGNOSIS—33% 1-year mortality, 75% 6-year mortality

ACUTE MANAGEMENT

ABC—O_2 to keep sat >95%, IV's

SYMPTOM CONTROL—★**LMNOP**★ ***L****asix/furosemide* 20–120 mg IV PRN, ***M****orphine* 2–5 mg IV PRN, ***N****itroglycerin* 0.4 mg SL PRN, **O_2**, **P**osition (upright)

LONG-TERM MANAGEMENT

★**DDDD**★

DIET—**low salt** (<100 mmol/day, 1.5–2 g/day), **fluid restriction** (1.5–2 L/day)

DIURETICS—***furosemide*** 20–120 IV/PO daily-BID with daily adjustments (try to use smallest dose possible to allow ACE inhibitor) ± ***metolazone*** 2.5–5 mg PO 30 min before furosemide, ***spironolactone*** 12.5–50 mg PO daily or ***eplerenone*** 25–50 mg PO daily **VASODILATORS**—**ACE inhibitor** (*captopril* 6.25–50 mg PO TID, *enalapril* 1.25–10 mg PO BID, *ramipril* 2.5–10 mg PO BID, *lisinopril* 2.5–20 mg PO daily, *perindopril* 2–8 mg PO daily). **ARB** (*valsartan* 40–160 mg PO BID, *candesartan* 8–32 mg PO daily). ***Hydralazine*** 10–50 mg PO QID and **nitrates** (*nitropatch* 0.4 mg topical daily or *isosorbide mononitrate* 30–90 mg PO daily). β-**blockers** (*metoprolol tartrate* 50–100 mg PO BID, *carvedilol* 3.125–25 mg PO BID, *bisoprolol* 2.5–10 mg PO daily)

DIGITALIS—***digoxin*** 0.0625–0.25 mg PO daily

TREAT UNDERLYING CAUSE—**CAD** (PCI/CABG), **aortic stenosis** (AV replacement), **sleep apnea** (CPAP)

DEVICES—if ejection fraction <30–35%, consider **cardiac resynchronization therapy** (CRT/biventricular pacing) ± **implantable cardioverter defibrillators** (ICD). **Ventricular assist devices** may also be considered in selected cases of refractory HF

TREATMENT ISSUES

ACE INHIBITOR (Garg, JAMA 1995)—hazard ratios for total mortality 0.77 and mortality/hospitalization 0.65 for any patients with LVEF <40%. Target dose = maximum tolerated. Contraindications include SBP <80 mmHg, bilateral renal artery stenosis, severe renal failure, and hyperkalemia

TREATMENT ISSUES (CONT'D)

ARB (CHARM)—consider substitution with ARB if ACE inhibitor *not tolerated* (e.g., cough). May also be used as adjunct to ACE inhibitor if β-blocker not tolerated. Contraindications similar to ACE inhibitor

HYDRALAZINE/NITRATES (VHEFT I and II, A-HeFT)—less effective than ACE inhibitor. Particularly useful for pregnant patients, African Americans, or those who developed renal insufficiency while on ACE inhibitor, or as add-on therapy

ANGIOTENSIN RECEPTOR–NEPRILYSIN INHIBITOR (McMurray, NEJM 2014, PARADIGM-HF)—combination sacubitril-valsartan demonstrated 16% reduction in all-cause mortality, 20% reduction in death from cardiovascular causes, and 21% reduction heart failure hospitalizations compared to enalapril

β-BLOCKERS (Foody JAMA 2002)—hazard ratios for total mortality 0.65 and mortality/hospitalization 0.64. May worsen symptoms in first few weeks and may take up to 1 year to see full effect in LVEF. Useful for patients with NYHA II–III (and stable IV) and LVEF <40%, also NYHA I, LVEF <40%, and post-MI. Contraindications include fluid overload and severe asthma. Start only when patient euvolemic

SPIRONOLACTONE (RALES 1999, EPHESUS 2003, EMPHASIS-HF 2011)—hazard ratios for all-cause mortality 0.7 and hospitalization for HF, 0.65 for patients with NYHA III–IV, LVEF <35%, and already on maximum medical therapy. Hazard ratios for cardiovascular death/HF hospitalization 0.63 and cardiovascular mortality 0.76 for patients with NYHA II and LVEF ≤30% (or LVEF 31–35% *plus* QRS duration >130 msec), and already on maximum medical therapy. Caution in elderly and renal failure patients as higher risk of hyperkalemia

DIGOXIN (DIG 1997)—hazard ratios for total mortality 0.99 and mortality/hospitalization 0.92. Particularly useful for patients with both HF and atrial fibrillation, or symptomatic HF despite maximum medical therapy

TREATMENT ISSUES (CONT'D)

OVERALL APPROACH—treat underlying cause if possible. Non-pharmacological treatments (diet, exercise, smoking cessation) → add ACE inhibitor if LVEF ≤40% (or hydralazine/nitrates if renal failure, ARB if cough secondary to ACE inhibitor) → add β-blocker when euvolemic if LVEF ≤40% → add spironolactone/eplerenone if NYHA II-IV if LVEF ≤30% (or ≤35% and QRS duration >130 msec) → add digoxin ± ARB if still symptomatic. If ejection fraction is <30–35% despite optimal medical therapy, consider revascularization, implantable cardioverter defibrillator, cardiac resynchronization (if QRS is wide), and ventricular-assist device/heart transplant

SPECIFIC ENTITIES

CAUSES OF FLASH PULMONARY EDEMA—**cardiac** (ischemic heart disease, acute aortic regurgitation, acute mitral regurgitation, mitral stenosis/obstruction, arrhythmia), **pulmonary** (pulmonary embolism, pneumonia), **renal** (bilateral renal artery stenosis), **systemic** (hypertension crisis, fever, sepsis, anemia, thyrotoxicosis)

HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY (HOCM)

- **PATHOPHYSIOLOGY**—autosomal dominant condition with mutated cardiac sarcomere, leading to massive ventricular hypertrophy (particularly septum). This results in left ventricular outflow tract obstruction, mitral regurgitation, diastolic dysfunction, and subsequently myocardial ischemia and overt heart failure. Cardiac arrhythmias may lead to sudden death (<1%/year). Other complications include atrial fibrillation and infective endocarditis
- **RISK FACTORS FOR SUDDEN DEATH**—major risk factors include history of cardiac arrest (VF), sustained VT, unexplained syncope, nonsustained VT on Holter, abnormal BP response on exercise test, left ventricular wall thickness >30 mm, and family history of sudden death. Minor risk factors include left ventricular outflow obstruction (gradient ≥30 mmHg), diastolic dysfunction, microvascular obstruction, late gadolinium enhancement on cardiac MRI, and high-risk genetic defect
- **CLINICAL FEATURES**—most are asymptomatic although dyspnea, chest pain, syncope, and sudden death may develop. Family history should be obtained. Physical findings include brisk carotid upstroke, bifid carotid pulse, double apical impulse, systolic ejection murmur (LLSB, louder with standing and Valsalva) ± mitral regurgitation murmur
- **DIAGNOSIS**—echocardiogram (septal thickening, systolic-anterior motion of mitral valve). Further workup includes 48 h Holter monitor and exercise testing annually
- **TREATMENTS**—**avoidance** (dehydration and strenuous exercise), **medical** (β-blockers and non-dihydropyridine calcium channel blockers as first line, disopyramide as second line), **interventional/surgical** (septal myomectomy, alcohol septal ablation, dual-chamber pacing), **prophylaxis** (implantable cardioverter defibrillator for high-risk patients to prevent sudden cardiac death, anticoagulation if atrial fibrillation)

NEJM 2004 350:13

Digoxin Intoxication — Circulation 2004 109:24

CAUSES

OVERDOSE—intentional, accidental (digoxin, foxglove, yellow oleander)

DRUG INTERACTIONS—quinidine, amiodarone, verapamil, diltiazem, tetracycline, erythromycin, rifampin, cyclosporine, SSRIs

PHARMACOKINETICS (see precipitants below)

CAUSES (CONT'D)

- **OLD AGE, RENAL FAILURE**
- **CARDIAC**—ischemia, myocarditis, cardiomyopathy, amyloidosis, cor pulmonale
- **METABOLIC**—hypokalemia, hypomagnesemia, hypernatremia, hypercalcemia, hypoxemia, acid–base imbalance

PATHOPHYSIOLOGY

DIGOXIN LEVEL—measurement of serum levels is not routinely necessary as dosing can usually be titrated according to clinical and hemodynamic effects. When measured, serum level should be collected at 12–24 h after the last dose (post-distribution phase). While the upper normal limit is 2.6 nmol/L [2.0 ng/mL], higher digoxin levels may be seen in asymptomatic patients. Low-dose digoxin, resulting in serum levels 0.5–0.9 nmol/L [0.4–0.7 ng/mL] is associated with possible survival benefit compared to ≥1 nmol/L [≥0.78 ng/mL] in HF patients

MECHANISM—digitalis acts by inhibiting the membrane-bound Na/K ATPase transport system. This leads to intracellular loss of K and gain of Na. Increase in intracellular Ca leads to ↑ cardiac contractility. Digoxin also exerts a vagotonic action, which slows conduction through the SA and AV node and helps to control heart rate

PRECIPITANTS OF DIGOXIN TOXICITY—toxicity is not merely related to serum levels, but also digoxin dosing (e.g., acute overdose), other medications (e.g., non-potassium sparing diuretics), and conditions (e.g., renal insufficiency, acute coronary syndromes, cardiac amyloidosis, hypothyroidism). For instance, hypokalemia, hypernatremia, hypomagnesemia and acidosis predispose to toxicity even at low-serum digoxin levels because of their depressive effects on the Na/K ATPase pump. In contrast, hyperkalemia occurs in acute toxicity and is directly related to prognosis

CLINICAL FEATURES

SIGNS AND SYMPTOMS

- **NEUROLOGICAL**—delirium, hallucination, blurred vision with altered color perception, headaches, dizziness
- **CARDIAC**—bradycardia, high-degree AV block, paroxysmal atrial tachycardia (often 2:1 AV conduction), unifocal or multifocal PVCs, bidirectional ventricular tachycardia, accelerated junctional tachycardia
- **GI**—anorexia, N&V, diarrhea, abdominal pain
- **METABOLIC**—hyperkalemia

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, Ca, Mg, albumin, serum digoxin level
- **ECG**
- **ABG**

DIAGNOSTIC ISSUES

ECG CHANGES ASSOCIATED WITH DIGOXIN

- **THERAPEUTIC LEVELS**—sagging of ST segments, flattened T waves, U waves, and shortened QT. Not to be confused with digoxin toxicity
- **TOXIC LEVELS**—first degree heart block, paroxysmal atrial tachycardia (often 2:1 AV conduction), regularized atrial fibrillation (i.e., with complete heart block), unifocal or multifocal PVCs, ventricular bigeminy, bidirectional VT

MANAGEMENT

ACUTE—ABC, **O_2**, IV, **treat arrhythmia**

TREAT UNDERLYING CAUSE—**observe**, **cardiac monitoring**, **activated charcoal** (if ingestion within 4 h). **Correct** electrolyte disturbances and reverse acidosis. **Atropine** for bradycardia. **Digibind**/**purified antidigoxin FAB fragments** (if acute ingestion of 10 mg or more in adults, or digoxin level >13 nmol/L [10 ng/mL], K >5 mM and life-threatening arrhythmia, hemodynamic instability, unstable arrhythmia [e.g., symptomatic bradycardia], or end-organ hypoperfusion [e.g., acute renal failure]). May see response in 20 min and complete response up to 4 h. Monitor potassium levels after treatment with Digibind)

TREATMENT ISSUES

AVOID

- **IV CALCIUM**—indicated for other causes of severe hyperkalemia, calcium may precipitate VT/sudden death and should **NOT** be given for hyperkalemia of digoxin toxicity
- **CARDIOVERSION**—relatively contraindicated because asystole or ventricular fibrillation may be precipitated
- **TRANSVENOUS PACING**—can precipitate arrhythmias and deterioration

HALF-LIVES—plasma $t_{½}$ for digoxin 1.6 days, digitoxin 5 days

INDICATIONS FOR DIGOXIN THERAPY—in patients with **symptomatic systolic HF and sinus rhythm** (digoxin may be especially useful in patients with severe symptoms despite standard medical therapy, LVEF <25%, or cardiomegaly), **diastolic HF** (with rapid atrial fibrillation or severe symptoms despite standard medical therapy), and **rapid atrial fibrillation** (with or without heart failure). Use with extreme caution or avoid in the elderly, patients with severe conduction abnormalities, acute coronary syndromes, or renal failure

Atrial Fibrillation

NEJM 2001 344:14; NEJM 2004 351:23
AHA/ACC/HRS 2014 Atrial Fibrillation Guidelines
Canadian Cardiovascular Society 2014 Atrial Fibrillation Guidelines

DIFFERENTIAL DIAGNOSIS OF PALPITATIONS

★PPP★

PHYSIOLOGIC (high output states)—anemia, pregnancy, fever, exercise, stress

PATHOLOGIC★CDE★

- **CARDIAC**—**arrhythmia** (see tachycardia below), **myocardial** (cardiomyopathy, atrial myxoma, shunts), valvular, transplanted heart
- **DRUGS**—sympathomimetic agents, vasodilators, anticholinergic agents, β-blocker withdrawal, illicit (cocaine, amphetamines)
- **ENDOCRINE**—hypoglycemia, hyperthyroidism, pheochromocytoma

PSYCHIATRIC—panic attack/disorder, generalized anxiety disorder, somatization disorder

DIFFERENTIAL DIAGNOSIS OF NARROW COMPLEX TACHYCARDIA

REGULAR NARROW COMPLEX TACHYCARDIA —sinus tachycardia, atrial flutter with fixed block (rate 300, 150, 100), supraventricular tachycardia (atrial tachycardia, AV nodal reentry, orthodromic AV reentrant/WPW), accelerated junctional tachycardia

IRREGULAR NARROW COMPLEX TACHYCARDIA—sinus tachycardia/arrhythmia, premature atrial contractions, multifocal atrial tachycardia, atrial flutter with variable block, atrial tachycardia with variable block, atrial fibrillation

DIFFERENTIAL DIAGNOSIS OF IRREGULARLY IRREGULAR RHYTHM

ATRIAL—sinus arrhythmia (rate 60–100), wandering pacemaker (rate 60–100), premature atrial rhythm/beat, multifocal atrial tachycardia (rate >100), ectopic atrial tachyarrhythmia with variable block, atrial flutter with variable block, atrial fibrillation

VENTRICULAR—premature ventricular contraction, polymorphic ventricular tachycardia, ventricular fibrillation

PATHOPHYSIOLOGY

CAUSES OF ATRIAL FIBRILLATION

- **CARDIOVASCULAR**—**myocardial** (hypertension, CAD, HF, hypertrophic cardiomyopathy, dilated cardiomyopathy, myocarditis, infiltration [amyloidosis, sarcoidosis, hemochromatosis], ASD), **valvular** (rheumatic, acquired, endocarditis), **arrhythmia** (WPW, SSS), **pericardial** (pericarditis), cardiac surgery
- **PULMONARY**—COPD, pulmonary embolism, pleural effusion
- **METABOLIC**—thyrotoxicosis, obesity
- **DRUGS**—theophylline, adenosine, digitalis, β-agonists, alcohol
- **IDIOPATHIC** (10%)

CLASSIFICATION OF ATRIAL FIBRILLATION

- **PAROXYSMAL ATRIAL FIBRILLATION**—episodes of AF last <7 days (usually <24 h). Terminates spontaneously or with intervention. May variably recur
- **PERSISTENT ATRIAL FIBRILLATION**—continuous AF sustained >7 days
- **LONG-STANDING PERSISTENT ATRIAL FIBRILLATION**—continuous AF >12 months
- **PERMANENT ATRIAL FIBRILLATION**—a classification determined by clinician and patient to stop further attempts to restore and/or maintain sinus rhythm. A therapeutic attitude rather than inherent pathophysiological attribute of AF
- **NONVALVULAR ATRIAL FIBRILLATION**—AF in the absence of rheumatic mitral stenosis, mechanical or bioprosthetic heart valve, or mitral valve repair
- **LONE ATRIAL FIBRILLATION**—AF in patients <60 years, no structural heart disease or risk factors, including hypertension

CLINICAL FEATURES OF NARROW COMPLEX TACHYCARDIA

HISTORY—palpitations, chest pain, dyspnea, dizziness, syncope, past medical history (AF, SVT, WPW, CAD, HF, hypertension, diabetes, stroke, TIA, thyroid dysfunction), medications (antihypertensives, antiarrhythmics), DVT/PE risk factors

PHYSICAL—vitals (pulse rate and rhythm, BP), cardiac and pulmonary examination for heart failure

CAROTID SINUS MASSAGE, VALSALVA, OR ADENOSINE—SVT may spontaneously terminate, while AF or atrial flutter may slow down. Avoid adenosine if suspect pre-excitation syndrome (atrial fibrillation or atrial flutter with WPW)

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT WITH PALPITATIONS HAVE A CARDIAC ARRHYTHMIA?

	Any arrhythmia		Significant arrhythmia	
	LR+	LR–	LR+	LR–
History				
Cardiac disease	2.03	0.71	0.42	1.07
Male sex	1.63	0.76	1.20	0.90
Age >60	1.70	0.83	1.89	0.77
Smoking >11/day	0.78	1.03	0.77	1.03
Anxiety disorder	0.98	1.01	0.92	1.04
FH of palpitations	0.86	1.04	1.07	0.98
EtOH >10 days/week	0.76	1.05	1.02	1.00
Panic disorder	0.26	1.30	–	–
Any psychiatric disorders	–	–	0.67	1.12
Palpitations				
Regular	1.66	–	1.38	0.55
Irregular	1.65	0.62	–	1.23
Duration >5 min	1.52	0.38	0.79	0.95
Duration >60 s	1.15	0.69	1.17	0.63
Continuous symptoms	1.06	–	0.93	1.20
HR >100/min	0.91	–	1.08	0.86
Precipitating factors				
Affected by sleep	2.29	0.70	2.44	0.63
Occurring at work	2.17	0.76	1.54	0.86
Caffeine	1.84	0.91	2.06	0.89
Occurs holiday	1.56	0.92	0.79	1.04
Occurs weekend	1.43	0.90	0.72	1.08
Alcohol	1.36	0.96	1.94	0.90
Lying in bed	1.30	0.61	1.02	0.97
Exercise	0.74	1.09	0.78	1.07
Breathing	0.52	1.23	0.52	1.20
While resting	–	–	1.02	0.97
Associated symptoms				
Regular rapid pounding sensation in neck	–	–	177	0.07
Neck fullness	–	–	0.85	1.04
Visible neck pulsations	–	–	2.68	0.87
Dizzy spells	0.93	1.08	1.34	0.67
Chest pain	0.81	1.07	0.92	1.02
Dyspnea	0.31	–	0.27	1.12
Vasovagal symptoms	–	–	1.72	0.63
Presyncope	–	–	1.04	0.95
Physical examination				
HR <60 or >100	–	–	3.00	0.78
Obesity	–	–	1.55	0.93
Hypertension	–	–	1.01	1.00

APPROACH—"while the presence of a regular rapid-pounding sensation in the neck or visible neck pulsations associated with palpitations makes the diagnosis of atrioventricular nodal reentry tachycardia likely, the reviewed studies suggest that the clinical examination is not sufficiently accurate to exclude clinically significant arrhythmias in most patients. Thus, prolonged electrocardiographic monitoring with demonstration of symptom-rhythm correlation is required to make the diagnosis of a cardiac arrhythmia for most patients with recurrent palpitations"

JAMA 2009 302:19

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, Mg, TSH, INR, PTT, D-dimer, troponin
- **IMAGING**—CXR, echocardiogram (enlarged left atrium)
- **ECG**
- **24-H HOLTER**
- **EXERCISE STRESS TEST**

SPECIAL

- **ELECTROPHYSIOLOGY STUDIES**

ACUTE MANAGEMENT

ABC—O_2 to keep sat >95%, IV

SYNCHRONIZED CARDIOVERSION—premedicate if possible with *midazolam* 1–2 mg IV q2–3 min, *fentanyl* 50–150 μg IV × 1, shock 50, 100, 200, 300, 360 J, prepare to intubate and give IV anti-arrhythmics PRN

AV NODAL BLOCKING AGENTS ★ABCD★

- **AMIODARONE**—*amiodarone* 150 mg IV bolus over 10 min, q10–15 min. Alternatively, infusion 60 mg/h over 6 h, then 30 mg/h over 18 h. Maximum 2.2 g/day
- **β-BLOCKERS**—*metoprolol* 5 mg IV over 1 min q5min × 3 PRN, *esmolol* 500 μg/kg IV over 1 min, maintenance dose 50–200 μg/kg/min IV
- **CALCIUM CHANNEL BLOCKERS**—*diltiazem* 15–20 mg IV over 2 min, repeat in 15 min at 20–25 mg PRN, maintenance dose 5–20 mg/h IV; *verapamil* 2.5–5.0 mg IV over 1–2 min, followed by 5–10 mg in 15–30 min PRN with maximum of 30 mg, maintenance dose 0.05–0.2 mg/min IV
- **DIGITALIS**—*digoxin* 0.25–0.5 mg IV q6h to a total dose of 1 mg, maintenance dose 0.125–0.25 mg PO/IV daily

OVERALL APPROACH

- **UNSTABLE ATRIAL FIBRILLATION**—perform cardioversion immediately
- **STABLE ATRIAL FIBRILLATION <48 H—rate control** (β-blockers, calcium channel blockers, digoxin) and consider **rhythm control** (DC cardioversion, amiodarone, propafenone, flecainide). Anticoagulate at least × 4 weeks post-cardioversion
- **STABLE ATRIAL FIBRILLATION >48 H OR UNKNOWN DURATION—rate control** (β-blockers, calcium channel blockers, digoxin) and consider **rhythm control** (IV unfractionated heparin → TEE to exclude atrial thrombus → cardioversion within 24 h → anticoagulate × 4 weeks; ALTERNATIVELY anticoagulate × 3 weeks → cardioversion → anticoagulate at least × 4 weeks)
- **TREAT UNDERLYING CAUSE/PRECIPITANT**—infection, myocardial infarction, ischemia, drugs, pulmonary embolism, thyrotoxicosis

LONG-TERM MANAGEMENT

RATE CONTROL—target resting HR <80 and exercise HR <110 in patients with significant symptoms. (Consider target resting HR <110 in asymptomatic patients with preserved LVEF). **β-blocker** (*metoprolol tartrate* [immediate release] 50–100 mg PO BID, *metoprolol succinate* [extended release] 100–200 mg PO daily, *carvedilol* 6.25–50 mg PO BID, *bisoprolol* 5–10 mg PO daily). **Calcium channel blockers** (*diltiazem CD* 120–480 mg PO daily). **Digitalis** (*digoxin* 0.5 mg PO × 1 dose, then 0.25 mg × 2 doses q6–12 h, then 0.0625–0.25 mg daily)

RHYTHM CONTROL—elective cardioversion (only after a 3-week course of therapeutic anticoagulation or atrial thrombus excluded by TEE. Cardioversion should be followed by 4 weeks of anticoagulation). **Antiarrhythmics** (*amiodarone* 200–400 mg PO daily, *sotalol* 40–160 mg PO BID, especially if CAD; *flecainide* 50 mg PO q12h, especially if no structural heart disease; *propafenone* 150 mg PO q8h, especially if no structural heart disease)

CLOT CONTROL—***ASA*** 81 mg daily if low-risk (nonvalvular disease and $CHADS_2 = 0$). Otherwise, **anticoagulation** (*warfarin* 5 mg PO daily to target INR between 2–3, *dabigatran* 110–150 mg PO BID, *rivaroxaban* 15–20 mg PO daily, *apixaban* 2.5–5 mg PO daily). Warfarin for AF with valvular disease. Novel anticoagulants (dabigatran, rivaroxaban, and apixaban) should not be used in patients with severe renal impairment, prosthetic heart valves, mitral stenosis, or valvular lesions associated with moderate to severe heart failure. Patients at higher risk of bleeding may require lower doses. Bridging anticoagulation (for initiation/interruption of warfarin therapy) not routinely required but should be considered in those at high risk for acute thrombosis (e.g., mechanical heart valves)

PROCEDURES—radiofrequency ablation of the pulmonary veins (PVI). Radiofrequency ablation of AV node with insertion of a permanent pacemaker and long-term anticoagulation as last resort. **Surgical** (corridor and maze procedures)

NEJM 2002 347:23; NEJM 2009 361:12; NEJM 2010 362:15; NEJM 2011 365:10; NEJM 2011 365:11

TREATMENT ISSUES

STROKE RISK FACTORS IN PATIENTS WITH ATRIAL FIBRILLATION

★CHADS2★

- **CHF** (any history, 1 point)
- **HYPERTENSION** (any history, 1 point)
- **AGE** ≥75 (1 point)
- **DIABETES** (1 point)
- **STROKE OR TIA** (2 points)

- **RISK OF STROKE (IF UNTREATED)**—0 points = 1.9%/year, 1 = 2.8%, 2 = 4.0%, 3 = 5.9%, 4 = 8.5%, 5 = 12.5%, 6 = 18.2%

★CHA2DS2-VASC★

- **CHF** (any history, 1 point)
- **HYPERTENSION** (any history, 1 point)
- **AGE** ≥75 (2 point)
- **DIABETES** (1 point)
- **STROKE OR TIA** (2 points)
- **VASCULAR DISEASE** (**coronary**, **aortic**, **or peripheral**) (1 point)
- **AGE 65–74** (1 point)
- **SEX, FEMALE** (1 point)

- **RISK OF STROKE (IF UNTREATED)**—0 points = 0%/year, 1 = 1.3%, 2 = 2.2%, 3 = 3.2%, 4 = 4.0%, 5 = 6.7%, 6 = 9.8%, 7 = 9.6%, 8 = 6.7%, 9 = 15.2%
- **OTHER RISK FACTORS**—CAD, echocardiography abnormalities (atrial size >5 cm, LV dysfunction), thyrotoxicosis, rheumatic valvular disease (RR 17). *All* mitral stenosis and HOCM patients with AF should have chronic anticoagulation (regardless of $CHADS_2$ or CHA_2DS_2-VASc score)
- **RISK REDUCTION**—ASA decreases risk by ~30%. Anticoagulation decreases risk of stroke by ~60%
- **FACTORS INCREASING RISK OF BLEEDING WITH WARFARIN USE**—advanced age, female sex, diabetes, prior hemorrhage, uncontrolled hypertension, alcoholism or liver disease, cancer, bleeding disorder, chronic kidney disease, ASA/clopidogrel/NSAIDs (including COX-2 inhibitors). Note that risk of fall by itself is not a contraindication to warfarin use
- **RISK OF BLEEDING ON ANTICOAGULATION**—as $CHADS_2$ score increases so does risk of major bleeding (but risk of stroke usually remains higher than risk of bleeding). Benefit-to-risk ratio for anticoagulation generally becomes even more favorable as risk factors for stroke accumulate. Risk calculation for bleeding usually unnecessary. Existing risk models do not reliably predict individual risk. Use clinical judgment

TREATMENT ISSUES (CONT'D)

★HASBLED★

- Hypertension, SBP >160 mmHg (1 point)
- Abnormal liver function (1 point)
- Abnormal renal function (1 point)
- Stroke (1 point)
- Bleeding tendency/predisposition (1 point)
- Labile INR on warfarin (1 point)
- Elderly, age >65 (1 point)
- Drugs (ASA, clopidogrel, NSAIDS) (1 point)
- Drugs (alcohol abuse) (1 point)

- **RISK OF BLEEDING**—0 = 1.13 bleeds/100 patient-years, 1 = 1.02, 2 = 1.88, 3 = 3.74, 4 = 8.70, 5 = 12.50, insufficient data for scores ≥6

IMPORTANT TOXICITIES OF AMIODARONE

- **CARDIAC** (5%)—sinus bradycardia and AV nodal block. QT prolongation leading to torsades de pointes may rarely occur
- **THYROID**—amiodarone-induced thyrotoxicosis (3%). Type 1 from increased thyroid hormone synthesis from excess iodine (usually with underlying multinodular goiter or Graves' disease). Type 2 from destructive thyroiditis and thyroid hormone release. Doppler US showing goiter and ↑ vascularity favors type 1 (hyperthyroidism), but normal sized gland and normal/↓ vascularity favor type 2 (thyroiditis). Presence of (any) radioiodine uptake favors hyperthyroidism (type 1), but absence of uptake does not reliably differentiate between type 1 or type 2. Patients on amiodarone may not develop classic symptoms of thyrotoxicosis; however, recurrence of AF should prompt investigation. Discontinuing amiodarone MAY paradoxically worsen thyrotoxicosis; treatment includes anti-thyroid drugs and steroids (for type 2). Hypothyroidism also common (20%)
- **PULMONARY** (<3%)—chronic interstitial pneumonitis (most common), cryptogenic organizing pneumonia, ARDS, and solitary pulmonary nodule. Histologically characterized by foamy macrophages in the air space. DLCO is often decreased. CT chest may show diffuse/localized interstitial or alveolar opacities. Treat with steroids and stop amiodarone

TREATMENT ISSUES (CONT'D)

- **HEPATIC** (15%)—non-alcoholic steatohepatitis which in severe cases may lead to cirrhosis
- **NEUROLOGIC** (30%)—ataxia, tremor, peripheral polyneuropathy, insomnia, and impaired memory
- **VISION** (100%)—corneal microdeposits may result in halo vision, photophobia, and blurred vision. Optic nerve injury (1–2%) may cause blindness
- **DERMATOLOGIC** (25–75%)—photosensitivity, gray-bluish discoloration (blue man syndrome), and alopecia. This is reversible upon discontinuation of amiodarone, but may take a few years

TREATMENT ISSUES (CONT'D)

- **MONITORING**—baseline TSH, LFTs, PFT and CXR. TSH and LFTs every 6 months, CXR yearly, and PFT as needed

NEJM 2007 356:9

Related Topics
ACLS (p. 495)
Digoxin (p. 43)
ECG (p. 73)
Wolff–Parkinson–White Syndrome (p. 76)

Syncope

See SYNCOPE (p. 353)

Cardiac Examination

PULSE

PULSUS TARDUS ET PARVUS (low carotid upstroke and amplitude)—aortic stenosis
BRISK PULSE (rapid carotid upstroke)—hypertrophic cardiomyopathy
BOUNDING PULSE (rapid carotid upstroke and descent)—↑ left ventricular volume (aortic regurgitation, mitral regurgitation, VSD, PDA, severe bradycardia), ↓ peripheral resistance (fever, anemia, thyrotoxicosis, rigid arteries, pregnancy)
PULSUS BISFERIENS (double-peaked)—combination aortic stenosis and regurgitation
REGULARLY IRREGULAR PULSE—sinus arrhythmia, pulsus bigeminus (PVC, PAC)
IRREGULARLY IRREGULAR PULSE—atrial fibrillation, premature atrial or ventricular contractions

BLOOD PRESSURE

CORRECT CUFF SIZE—width of bladder ≥40% of arm circumference and length of bladder ≥80% of arm circumference
AUSCULTATORY GAP—defined as the gap between the first Korotkoff sound (which may disappear briefly) and its reappearance. Missing the higher reading can lead to an underestimation of systolic blood pressure. Thus, the systolic blood pressure should always be palpated first before auscultation

BLOOD PRESSURE (CONT'D)

WIDE PULSE PRESSURE—isolated systolic hypertension, aortic regurgitation, hyperdynamic states (sympathetic hyperactivity, fever/sepsis, anemia, thyrotoxicosis, large AV fistula, PDA, beriberi, pregnancy)
PSEUDOHYPERTENSION—false elevation of systolic blood pressure secondary to rigid arteries. The Osler's maneuver may be useful for determining the presence of pseudohypertension
PULSUS ALTERNANS (alternating fluctuation in pulse pressure)—initially hear only the more prominent beats. As cuff pressure decreases, start to hear the less intense beats (1:1 ratio). This may be detected in severe LV dysfunction and aortic stenosis
PULSUS PARADOXUS—inspiratory drop in systolic blood pressure >10 mmHg. Causes include asthma, COPD, **tamponade**, restrictive cardiomyopathy, constrictive pericarditis, hypovolemic shock, and rarely pulmonary embolism, SVC obstruction, and morbid obesity

JUGULAR VENOUS PRESSURE

A WAVE—atrial contraction

- **PROMINENT A WAVE**—tricuspid stenosis, pulmonary stenosis, pulmonary hypertension, hypertrophic cardiomyopathy, and Ebstein's anomaly
- **CANNON A WAVE**—AV dissociation (complete heart block, ventricular tachycardia) (right atrium contracts against closed tricuspid valve)
- **DECREASED A WAVE**—dilated right atrium
- **ABSENT A WAVE**—atrial fibrillation

X DESCENT—atrial relaxation. S1 starts

- **DECREASED X DESCENT**—atrial fibrillation
- **X DESCENT DEEPER THAN Y DESCENT**—tamponade

C WAVE—bulging of tricuspid valve into right atrium during ventricular isometric contraction

X' DESCENT—descent of the base of the heart during systole

V WAVE—atrial filling. S2 just before peak of v

- **DOMINANT V WAVE**—tricuspid regurgitation (cv wave), right heart failure, atrial septal defect

Y DESCENT—opening of tricuspid valve/atrial emptying

- **RAPID STEEP Y DESCENT**—constrictive pericarditis (square root sign), severe right heart failure
- **DECREASED Y DESCENT**—tricuspid stenosis
- **BLUNTED/ABSENT Y DESCENT**—tamponade

ABDOMINOJUGULAR REFLUX (AJR)—blood pressure cuff pumped 6×, then pressed against abdomen at 20–35 mmHg for 15–30 s. Positive AJR occurs when abdominal compression causes a sustained increase in JVP >4 cm [>1.6 in.] and predicts elevated left atrial pressure (≥15 mmHg, LR+ 8.0, LR– 0.3)

KUSSMAUL SIGN—paradoxical increase in JVP during inspiration. Causes include right ventricular failure, restrictive cardiomyopathy, constrictive pericarditis, SVC obstruction, and pulmonary embolism

PRECORDIAL EXAMINATION

INSPECTION—apex, right ventricular heave

PALPATION—apex, heaves, thrills, palpable heart sounds

- **DISPLACED APICAL BEAT** (lateral to mid-clavicular line)—left ventricular dilatation, LR+ 8.0
- **ENLARGED APICAL BEAT** (≥2.5 cm)—left ventricular dilatation, LR+ 4.7

PRECORDIAL EXAMINATION (CONT'D)

- **SUSTAINED APICAL BEAT** (outward impulse extends to, or past, S2)—left ventricular pressure overload (aortic stenosis), volume overload (aortic regurgitation, VSD), severe cardiomyopathy, or ventricular aneurysm
- **RETRACTING APICAL BEAT** (retraction during systole; inward motion begins at S1, outward impuse after S2)—constrictive pericarditis (up to 90%), tricuspid regurgitation
- **SUSTAINED LEFT PARASTERNAL MOVEMENT** ("lift/heave")—tricuspid regurgitation, mitral regurgitation
- **PALPABLE P2**—pulmonary hypertension in mitral stenosis, LR+ 3.6

HEART SOUNDS

TECHNIQUE—S1, S2, and physiological splitting of S2 are best heard over the base. Identification of S3 and S4 requires conscious effort listening for low pitched sounds over the apex (using the bell)

DISTINGUISHING S1 FROM S2—time with carotid pulse, diastole longer than systole, S2 louder than S1 at the base, S1 is low pitched and longer while S2 is high pitched and shorter, S2 often split

INTENSITY OF S1 AND S2

- **LOUD P2 >A2 AT PULMONIC AREA**—increased pulmonary pressure (left ventricular failure, mitral stenosis, pulmonary hypertension), increased pulmonary flow (atrial septal defect)
- **LOUD S2 AT AORTIC AREA**—hypertension, hyperdynamic states (fever, hyperthyroidism, anemia)
- **SOFT S2 OVER AORTIC AREA**—severe aortic stenosis
- **LOUD S1 AT MITRAL AREA**—mitral stenosis
- **SOFT S1**—mitral regurgitation, left bundle branch block, short PR interval

SPLITTING OF S2

- **FIXED SPLITTING** (splitting same degree during both inspiration and expiration)—atrial septal defect, right ventricular failure
- **WIDE SPLITTING** (splitting greater during inspiration than expiration)—right bundle branch block, pulmonary stenosis, pulmonary hypertension
- **PARADOXICAL (REVERSED) SPLITTING** (splitting only during expiration)—left bundle branch block, severe aortic stenosis, RV pacing

NORMAL AND EXTRA HEART SOUNDS

Sound	Heard	Pitch	Others
S1	LUSB	High	
Early systolic click	RUSB	High	Aortic stenosis
Mid-systolic click	Apex	High	MVP, louder standing
S2	LUSB	High	Splitting

HEART SOUNDS (CONT'D)

Sound	Heard	Pitch	Others
Opening snap (early diastolic)	Apex	High	Mitral stenosis
S3 (early diastolic)	Apex	Low	Heart failure
S4 (late diastolic)	Apex	Low	HTN, aortic stenosis

HEART SOUNDS (CONT'D)

High pitch sounds are best heard with the diaphragm, while low pitch sounds are best heard with the bell

DISTINGUISHING FEATURES BETWEEN P2 AND OPENING SNAP

1. P2 is best heard at LUSB while opening snap is best heard at the apex
2. P2 separates from A2 on inspiration, while opening snap tends to move closer to S2 on inspiration

DISTINGUISHING FEATURES BETWEEN S4 AND S1

1. S4 is usually best heart at apex with the bell while S1 is best heard at base
2. S4 is usually more widely separated from S1 than splitting of S1
3. S4 is loudest at the start of expiration, softest at mid-inspiration
4. S4 may be accentuated by lying down, exercise, or forced inspiration with closed glottis
5. S4 has a lower pitch than S1

DISTINGUISHING FEATURES BETWEEN S3 AND OPENING SNAP

1. S3 has a lower pitch than opening snap
2. S3 occurs later than opening snap

DISTINGUISHING FEATURES BETWEEN S3 AND S4

1. S3 has a lower pitch than S4
2. S3 is closer to S2 while S4 is closer to S1
3. Left ventricular S3 is louder at the apex while right ventricular S3 or S4 is usually best heart at left sternal border or at the base

MURMURS

TIMING

- **MID-SYSTOLIC**—aortic stenosis, aortic sclerosis, pulmonary stenosis, hypertrophic obstructive cardiomyopathy, atrial septal defect, flow murmurs (fever, pregnancy, hyperthyroidism, anemia, aortic regurgitation due to high flow)
- **PANSYSTOLIC**—mitral regurgitation, tricuspid regurgitation, ventricular septal defect, aortopulmonary shunts
- **LATE SYSTOLIC**—mitral valve prolapse, papillary muscle dysfunction
- **EARLY DIASTOLIC**—aortic regurgitation, pulmonary regurgitation

MURMURS (CONT'D)

- **MID-DIASTOLIC**—mitral stenosis, tricuspid stenosis, atrial myxoma, Austin Flint murmur of aortic regurgitation, Carey Coombs murmur during acute phase of rheumatic fever
- **PRE-SYSTOLIC**—mitral stenosis, tricuspid stenosis, atrial myxoma
- **CONTINUOUS MURMURS**—patent ductus arteriosus, arteriovenous fistula, aortopulmonary connection, venous hum, mammary souffle

INTENSITY—grade I (barely audible), grade II (faint but can be heard immediately), grade III (easily heard), grade IV (loud AND associated with palpable thrill), grade V (very loud, can be heard with the stethoscope half off chest), grade VI (very loud, can be heard with stethoscope off chest wall)

QUALITY—depends on the pitch, may be musical, harsh, blowing, rumbling, scratchy, grunting, or squeaky

CONFIGURATION—crescendo, decrescendo, crescendo–decrescendo, plateau, holosystolic

LOCATION—aortic valve (RUSB), pulmonary valve (LUSB), tricuspid valve (LLSB), mitral valve (apex)

RADIATION—aortic valve (carotids), pulmonary valve (left shoulder), tricuspid valve (xyphoid, right of sternum), mitral valve (axilla)

MANEUVERS

- **RESPIRATION**—**right-sided** murmurs typically increase with inspiration (except pulmonic click) or sustained abdominal pressure (↑ venous return), while **left-sided** murmurs are generally louder during expiration
- **VALSALVA MANEUVER** (↓ venous return and ↑ systemic arterial resistance)—most murmurs decrease in length and intensity during the Valsalva maneuver. Two exceptions are the systolic murmur of **hypertrophic cardiomyopathy**, which usually becomes much louder, and the systolic murmur of **mitral valve prolapse**, which becomes longer and often louder (click moves closer to S1)
- **POSITIONAL CHANGES**—most murmurs diminish with standing due to reduced preload. However, the murmur of **hypertrophic cardiomyopathy** becomes louder and the murmur of **mitral valve prolapse** lengthens and often is intensified. Squatting (or usually passive leg raising, both ↑ venous return and ↑ systemic arterial resistance) produces opposite effect

MURMURS (CONT'D)

- **ISOMETRIC EXERCISE** (↑ systemic arterial resistance)—murmurs caused by blood flow across normal or obstructed valves (e.g., **mitral or pulmonic stenosis**) become louder. Murmurs of **mitral and aortic regurgitation** and **ventricular septal defect** also increase with handgrip exercise

MURMURS (CONT'D)

- **TRANSIENT ARTERIAL OCCLUSION** (↑ systemic arterial resistance)—transient external compression of both arms by bilateral cuff inflation to 20 mmHg greater than peak systolic pressure augments the murmurs of **mitral regurgitation**, **aortic regurgitation**, **and ventricular septal defect**, but not murmurs due to other causes

DISTINGUISHING FEATURES AMONG COMMON SYSTOLIC AND DIASTOLIC MURMURS

	Systolic murmurs						**Diastolic murmurs**			
Findings[a]	**Tricuspid regurgitation**	**Mitral valve prolapse**	**Mitral regurgitation**	**Aortic sclerosis**	**Aortic stenosis**	**Hypertrophic cardiomyopathy**	**Tricuspid stenosis**	**Pulmonary regurgitation**	**Mitral stenosis**	**Aortic regurgitation**
Inspection	Dyspnea Cyanosis Cachexia Jaundice	Pectus excavatum Marfan's scoliosis	Dyspnea	Normal	Dyspnea Sustained apex	Dyspnea Double apex	Normal	Dyspnea	**Mitral facies** Cyanosis Dyspnea	Argyll Robertson Marfan's Ank. Spond
Radial pulse	Irregular (AF)	Normal	Irregular (AF)	Normal	**Brachio-radial delay**	Brisk	Irregular (AF)	Normal	**Irregular** (AF)	**Water-hammer**
BP	Normal	Normal	Normal	Normal	Narrow PP	Normal	Normal	Normal	**Narrow PP**	**Wide PP**
Carotid	Normal	Normal	Bounding Irregular (AF)	Normal	**Pulsus parvus et tardus**	**Brisk bifid**	Irregular (AF)	Normal	**Irregular** (**AF**)	**Bounding/ collapsing pulse**
JVP	Increased **V wave** Prominent a wave (pul. HTN), no a wave (AF)	Normal	Absent a wave (AF)	Normal	Normal	Prominent a wave	**Prominent a wave**, **slow y descent**, absent a wave (AF)	Prominent a wave (pul. HTN)	Absent a wave (AF) Prominent a wave (pul. HTN), cv wave (TR)	Normal
Palpation	Palpable P2 (pul. HTN), thrill RV heave	Normal	Enlarged, displaced apex, thrill RV heave	Normal	Sustained apex, thrill LV heave	**Double apical impulse** Thrill LV heave	Normal	Palpable P2 (pul. HTN), thrill RV heave	RV heave Palpable P2 (pul. HTN)	Sustained, displaced apex, thrill LV heave
S1[b]	Soft	Normal	Soft	Normal	Normal	Normal	Wide splitting S1	Normal	**Loud S1**	Split (chronic) Absent (acute)
S2[b]	Loud (pul. HTN)	Normal	Normal	Normal	**Paradoxical split**, **soft**	Paradoxical split	Normal	Loud (pul. HTN)	**Palpable P2** (**pul. HTN**)	Soft
S3	R sided	Normal	L sided	Normal	Normal	**L sided**	Normal	R sided	**Absent**	L sided
S4	None	Normal	Normal	Normal	**L sided**	**L sided**	Normal	R sided	Normal	L sided
Clicks or snaps	None	**Mid-systolic click**	None	None	Early systolic click	None	Opening snap (LSB)	None	**Opening snap** (apex)	None
Murmur[c]	LLSB High pitch Holosystolic	Apex High pitch **Late** systolic	Apex High pitch **Holo**systolic	RUSB High pitch Mid-systolic	RUSB High pitch Mid-systolic	**LLSB**, apex High pitch Mid-systolic	LLSB **Low pitch** Mid-diastolic	LUSB High pitch Early diastolic	Apex **Low pitch** Mid-diastolic[e]	RUSB High pitch Early diastolic
Radiation	Xyphoid	None	Axilla	None	Clavicle Carotids	Base of heart	None	None	None	Apex Sternum
Maneuvers	↑ **inspiration**, **sustained Abdominal pressure**	↑ **standing**, **Valsalva**[d] ↓ **squatting**	↑ isometric, transient art. occlusion	None	↑ squatting, leg raise ↓ standing, Valsalva, isometric	↑ **standing**, **Valsalva** ↓ **squatting**	↑ inspiration	↑ inspiration	↑ isometric ↓ standing, Valsalva	↑ isometric, transient art. occlusion, Best heard sitting up in end expiration
Other associated murmurs/ clinical features	**Graham Steell murmur** (pul. HTN) Ascites, pulsatile liver, edema	Mitral regurgitation (holosystolic at apex)	Pulmonary edema	None	**Gallavardin phenomenon** (mid-systolic murmur at apex)	Mitral regurgitation (mid-systolic at apex)	Mitral stenosis may also be present	PR murmur called **Graham Steell m**. if secondary to pul. HTN	**Pulmonary and tricuspid regurg. Murmurs** (pul. HTN)	**Austin Flint Murmur** (mid-diastolic over apex) Mid-systolic **flow** m. Other signs[f]

[a]Not all findings listed for each condition may be present on examination

[b]Loud heart sounds are usually due to mild-moderate stenotic lesions, while light heart sounds are usually due to regurgitant or severe stenotic lesions

[c]Regurgitant murmurs usually start early, while stenotic murmurs tend to start mid-way

[d]For mitral valve prolapse, maneuvers that increase murmur intensity also move both the click and murmur closer to S1

[e]For mitral stenosis, the murmur is classically described as mid-diastolic with presystolic accentuation

[f]All the following special signs for aortic regurgitation are related to increased pulse pressure. These include Quincke's sign (pulsatile refill in capillary bed of finger nails), Becker's sign (pulsatile retinal artery), deMusset's sign (head bob), Mueller's sign (pulsatile uvula), Mayne's sign (DBP ↓ 15 mmHg with arm raised), Gerhardt's sign (pulsatile spleen), Rosenbach's sign (pulsatile liver), Traube's sign (pistol shot sound over femoral arteries), Duroziez's sign (femoral artery bruit with compression), Hill's sign (popliteal SBP > brachial SBP by 60 mmHg)

MURMURS (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE AN ABNORMAL SYSTOLIC MURMUR?

AORTIC STENOSIS—"presence of any of following significantly increases the likelihood of aortic stenosis: effort syncope, slow carotid upstroke, late or mid peaking systolic murmur, decreased or absent S2, apical-carotid delay, brachioradial delay." "The presence of AS requires detection of a systolic murmur, generally radiating to the right clavicle."

Update for Clinical Signs for Detecting Aortic Stenosis

	LR+	LR–
Slow carotid upstroke	9.2	0.56
Murmur radiating to right carotid	8.1	0.29
Reduced or absent S2	7.5	0.50
Murmur over the right clavicle	3.0	0.10
Reduced carotid volume	2.0	0.64

The Rational Clinical Examination. Mcgraw-Hill, 2009

MITRAL REGURGITATION—"for cardiologists, absence of a mitral area murmur or a late systolic/holosystolic murmur significantly reduces the likelihood of mitral regurgitation, except in the setting of acute MI. Cardiologists can accurately distinguish left-sided regurgitant murmurs, such as mitral regurgitation and ventricular septal defect, using transient arterial occlusion"

TRICUSPID REGURGITATION—"cardiologists can accurately detect the murmur of tricuspid regurgitation. Cardiologists can accurately rule in and rule out tricuspid regurgitation using the quiet inspiration and sustained abdominal pressure maneuvers"

HYPERTROPHIC CARDIOMYOPATHY—"cardiologists can rule in or rule out hypertrophic cardiomyopathy by evaluating for decreased murmur intensity with passive leg elevation or increased murmur intensity when the patient goes from a **squatting to standing position**"

MITRAL VALVE PROLAPSE—"a **systolic click, with or without systolic murmur**, is sufficient for the diagnosis of mitral valve prolapse. The absence of both a systolic click and murmur significantly reduces the likelihood of echocardiographic mitral valve prolapse. In patients with echocardiographic mitral valve prolapse, a holosystolic murmur without a systolic click significantly increases the likelihood of long term complications, whereas absence of both a systolic click and murmur significantly reduces the likelihood of long term complications"

JAMA 1997 277:7

MURMURS (CONT'D)

INNOCENT MURMURS—in otherwise healthy younger patients. Systolic murmurs tend to be mid-systolic, grade 1 or 2 (possibly 3), loudest over LUSB, and do not radiate. Murmurs that are associated with systolic thrill (LR+ 12), holosystolic (LR+ 8.7), loud (LR+ 6.5), or plateau-shaped (LR+ 4.1) are more likely to be significant. Diastolic murmurs are always abnormal

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE AORTIC REGURGITATION?

AORTIC REGURGITATION—"when a cardiologist hears the typical murmur of aortic regurgitation, the likelihood of mild or greater aortic regurgitation is increased significantly. The absence of a typical **diastolic murmur** significantly reduces the likelihood of aortic regurgitation"

MITRAL STENOSIS—"presence of a **mid-diastolic murmur** significantly increases the likelihood of mitral stenosis, while absence of a mid-diastolic murmur significantly reduces the likelihood of mitral stenosis"

PULMONARY REGURGITATION—"when a cardiologist hears a typical pulmonary regurgitation murmur, the likelihood of pulmonary regurgitation increases significantly. Absence of a typical murmur does not alter the likelihood of pulmonary regurgitation"

JAMA 1999 281:23

INVESTIGATIONS

ECHOCARDIOGRAM—if cardiac symptoms, murmur grade ≥3, diastolic murmur, or when other cardiac findings are present

Aortic Stenosis

AHA/ACC Valvular Heart Disease 2014 Guidelines
Lancet 2009 373:9667; NEJM 2002 346:9

DIFFERENTIAL DIAGNOSIS

VALVULAR

- **CONGENITAL MALFORMATIONS**—unicuspid, bicuspid
- **CALCIFICATION**—degenerative or senile, atherosclerosis, Paget's disease, chronic renal failure
- **INFECTIONS**—rheumatic fever, *Chlamydia pneumoniae*
- **RHEUMATOID ARTHRITIS**

SUBVALVULAR

- **DISCRETE LESIONS**—membranous diaphragm, fibromuscular ring
- **OBSTRUCTIVE**—hypertrophic cardiomyopathy

SUPRAVALVULAR—localized or discrete narrowing of the ascending aorta (Williams' syndrome)

LOW GRADIENT AORTIC STENOSIS—resulting from low cardiac output

PATHOPHYSIOLOGY

COMPLICATIONS ★BEE★

- **B**leeding (angiodysplasia + aortic stenosis + acquired vWD type IIa = Heyde's syndrome)
- **E**ndocarditis
- **E**mbolic events (cerebral, systemic)

CLINICAL FEATURES

PHYSICAL—tachypnea, decreased pulse pressure, brachioradial delay, pulsus parvus et tardus (slow rise and low amplitude), apical-carotid delay, hyperdynamic apical beat, systolic thrill at the base of heart, narrowly split or paradoxical splitting of S2 or absent S2, harsh mid-systolic ejection murmur (radiation to carotids), Gallavardin phenomenon

GALLAVARDIN PHENOMENON—aortic stenosis murmur is usually harsh and loudest over the right upper sternal border, whereas a Gallavardin murmur is musical and may be heard over apex. It is due to radiation of the high-frequency components of the aortic stenosis murmur to the apex

DISTINGUISHING FEATURES BETWEEN AORTIC SCLEROSIS AND AORTIC STENOSIS MURMUR

	Aortic sclerosis	Aortic stenosis
Pathophysiology	Abnormally thickened valve leaflets but minimal outflow obstruction	Decreased functional area of valve to cause decreased outflow
Carotid pulse	Normal	Pulsus parvus et tardus
S2	Normal	Soft single S2 (P2)
Murmur	Mid-systolic murmur	Late peaking of systolic murmur

DISTINGUISHING FEATURES BETWEEN AORTIC STENOSIS, MITRAL REGURGITATION, AND HYPERTROPHIC CARDIOMYOPATHY

	Aortic stenosis	Mitral regurgitation	HOCM
Carotid upstroke	Slow, low amplitude	Normal or low amplitude	Brisk
S1	Normal	Soft	Normal
S2	Single if severe	Normal	Often reversed
S3	No	Loud	No
S4	If severe	No	Yes
Loudest murmur	RUSB	Apex	LLSB and apex
Maneuvers			
Standing	↓	↓	↑
Squatting	↑	↑	↓
Valsalva	↓	↓	↑

INVESTIGATIONS

BASIC

- **CXR**
- **ECHOCARDIOGRAM**—transthoracic
- **ECG**—left ventricular hypertrophy
- **EXERCISE TESTING**

SPECIAL

- **CARDIAC CATHETERIZATION**

DIAGNOSTIC AND PROGNOSTIC ISSUES

AORTIC VALVE AREA AND SEVERITY

- **NORMAL** = peak velocity <2 m/s, area = 3–4 cm^2
- **MILD** = peak velocity 2.0–2.9 m/s, mean gradient <20 mmHg, area = 1.5–2 cm^2
- **MODERATE** = peak velocity 3.0–3.9 m/s, mean gradient 20–39 mmHg, area = 1–1.5 cm^2
- **SEVERE** = peak velocity ≥4 m/s, mean gradient >40 mmHg, area = ≤1 cm^2 (or indexed area ≤ 0.6 cm^2/m^2)
- **SYMPTOMS**—usually do not appear until valve ≤1 cm^2. The significance of valve area depends on patient size (larger patient = more severe for same valve area)
- **PROGRESSION**—valve area decreases by ~0.1 cm^2/year and the mean gradient increases by 7 mmHg/year (particularly if cardiac risk factors)

PROGNOSIS OF AORTIC STENOSIS ★ASH★
(**A**ngina, **S**yncope, **H**eart failure)

- **SEVERE AORTIC STENOSIS WITH NO SYMPTOMS**—1–2% DIE IN SHORT PERIOD
- **SEVERE AORTIC STENOSIS WITH ANGINA PRESENTATION**—50% DIE IN 5 YEARS
- **SEVERE AORTIC STENOSIS WITH SYNCOPE PRESENTATION**—50% DIE IN 3 YEARS
- **SEVERE AORTIC STENOSIS WITH HEART FAILURE PRESENTATION**—50% DIE IN 2 YEARS
- **SEVERE AORTIC STENOSIS AFTER VALVE REPLACEMENT**—survival similar to normal individuals

MANAGEMENT

MILD OR MODERATE AORTIC STENOSIS—follow clinically and with echocardiogram (every 3–5 years for mild, every 1–2 years for moderate, every year for severe)

SEVERE OR SYMPTOMATIC AORTIC STENOSIS—**aortic valve replacement** (transcatheter or surgical, see criteria below), balloon valvuloplasty (offers no survival benefit and is only a temporizing measure until surgical or percutaneous aortic valve replacement can be performed)

VASODILATORS—use with caution in the setting of hypertension or HF. ACE inhibitors

MANAGEMENT (CONT'D)

preferred over β-blockers because of risk of reduced inotropy; start low dose and titrate slowly; risk of hypotension and syncope

TREATMENT ISSUES

AORTIC VALVE REPLACEMENT (AVR)

- **RECOMMENDED INDICATIONS** (**CLASS I**)—if severe AS with symptoms of HF, syncope, exertional dyspnea, angina, or presyncope (by history or on exercise testing); asymptomatic severe AS and LVEF <50%; or severe AS and undergoing cardiac surgery for other reasons
- **REASONABLE INDICATIONS** (**CLASS IIa**)—if asymptomatic but *very* severe AS (i.e., peak velocity ≥5 m/s or mean gradient ≥60 mmHg); severe AS and exercise test with ↓ exercise tolerance or ↓ in SBP; symptomatic low-flow/low-gradient severe AS (i.e., valve area ≤1 cm^2) with LVEF <50%, and severe/high gradients on dobutamine stress test; symptomatic low-flow/low-gradient severe AS (i.e., valve area ≤1 cm^2) with normal LVEF ≥50% and valve obstruction as most likely cause of symptoms (based on clinical, hemodynamic, and anatomic data); or moderate AS and undergoing cardiac surgery for other reasons
- **POSSIBLE INDICATIONS** (**CLASS IIb**)—if severe AS and rapid disease progression and low surgical risk
- **PREOPERATIVE CONSULT**—AVR should be done before elective non-cardiac surgeries in symptomatic patients
- **RISK OF AVR**—mortality 1–2%, morbidity 1%/year (venous thromboembolic disease, bleeding, deterioration of prosthetic valve, endocarditis)

SURGICAL VS. TRANSCATHETER VALVE—transcatheter aortic valve replacement (TAVR) should be considered for patients with an indication for AVR who have high or prohibitive surgical risk for surgical AVR. A multidisciplinary heart valve team should collaborate in the decision making process

MECHANICAL VS. BIOPROSTHETIC VALVE—compared to human tissue valves, mechanical valves have prolonged durability, but higher chance of thromboembolism and bleeding from chronic anticoagulation. Overall, long-term outcomes are better with a mechanical valve. Main indications for bioprosthesis valve include patients who cannot or will not tolerate warfarin or for whom compliance is uncertain, patients ≥65 years of age who do not have risk factors for thromboembolism, and women of childbearing age

Aortic Regurgitation AHA/ACC Valvular Heart Disease 2014 Guidelines

DIFFERENTIAL DIAGNOSIS

VALVE ABNORMALITY—rheumatic heart disease, infective endocarditis, SLE, calcifications, congenital (bicuspid or unicuspid aortic valve), flail leaflet, osteogenesis imperfecta, drugs (fenfluramine)

AORTIC DILATION—aortic dissection, ankylosing spondylitis, syphilis, Marfan's, Ehlers Danlos, hypertension, bicuspid aortic valve, cystic medial necrosis

PATHOPHYSIOLOGY

PATHOPHYSIOLOGY—leaky aortic valve → initial compensation with left ventricular dilatation and eccentric hypertrophy (palpitations, atypical chest pain), wide pulse pressure (due to increased stroke volume with elevation in SBP and regurgitation with rapid collapse of the arteries and a low diastolic blood pressure) → eventually decompensation leading to left ventricular dysfunction (heart failure)

CLINICAL FEATURES

PHYSICAL

- **GENERAL APPEARANCE**—Marfan's syndrome, ankylosing spondylitis, Argyll Robertson pupils, **Quincke's sign** (pulsatile refill in capillary bed of finger nails), digital throb, **Becker's sign** (visible pulsations of the retinal arteries and pupils), **deMusset's sign** (head bob occurring with each heart beat), **Mueller's sign** (systolic pulsations of the uvula)
- **VITALS**—wide pulse pressure, **water hammer** (tapping impulse in forearm, especially when arm is raised vertically), **Corrigan's pulse**, **Mayne's sign** (>15 mmHg decrease in diastolic blood pressure with arm elevation)
- **CARDIAC**—soft S1, left-sided S3 (heart failure), **diastolic murmur** (early diastolic or holodiastolic, blowing, over left upper sternal border), **Austin Flint murmur** (mid/late diastolic rumble, over apex) and **mid-systolic flow murmur**
- **OTHERS**—**Gerhardt's sign** (systolic pulsations of the spleen), **Rosenbach's sign** (systolic pulsations of the liver), **Traube's sign** (pistol shot pulse with systolic and diastolic sounds heard over the femoral arteries), **Duroziez's sign** (systolic and diastolic bruit heard when the femoral artery is partially compressed), **Hill's sign** (popliteal cuff systolic pressure exceeding brachial pressure by >60 mmHg). Note that all the special signs are due to increased pulse pressure

DISTINGUISHING FEATURES BETWEEN AORTIC REGURGITATION AND PULMONARY REGURGITATION MURMUR

- **PULMONARY REGURGITATION MURMUR**—high pitch decrescendo diastolic murmur (Graham Steell murmur) loudest over **left upper sternal border. Increases with inspiration**. May be associated with signs of pulmonary hypertension
- **AORTIC REGURGITATION MURMUR**—early diastolic decrescendo murmur loudest over **right and/or left upper sternal border**. No change or decreases with inspiration. May be associated with **Austin Flint murmur** and the other signs of aortic regurgitation

DISTINGUISHING FEATURES BETWEEN AUSTIN FLINT AND MITRAL STENOSIS MURMUR

	Austin Flint	Mitral stenosis
Gender	M > F	F > M
Hemoptysis	Almost never	Likely mitral stenosis
Rhythm	Sinus	Atrial fibrillation
M1	Usually faint	Usually loud
P2	Normal or ↑	Usually loud
Ventricular gallop/S3	Always present	Absent
Diastolic murmur	Usually early or mid-diastolic	Often presystolic accentuation (if in sinus rhythm)
Opening snap	Absent	Present
CXR	Boot shaped	LAE
ECG	Sinus, LVH, prolonged PR	Atrial fibrillation, P mitrale

INVESTIGATIONS

BASIC

- **CXR**—cardiomegaly
- **ECHOCARDIOGRAM**
- **ECG**—LVH
- **EXERCISE TESTING**

SPECIAL

- **CARDIAC CATHETERIZATION**

PROGNOSTIC ISSUES

ASYMPTOMATIC WITH NORMAL LV SYSTOLIC FUNCTION

- **PROGNOSIS**—development of symptoms and/or LV dysfunction <6%/year; asymptomatic LV dysfunction <3.5%/year; sudden death <0.2%/year

ASYMPTOMATIC WITH LV DYSFUNCTION

- **PROGNOSIS**—progression to cardiac symptoms >25%/year

SYMPTOMATIC

- **PROGNOSIS**—mortality >10%/year

MANAGEMENT

LIFESTYLE CHANGES—salt restriction/diuretics

MEDICATIONS—afterload reduction with vasodilators (nifedipine, ACE inhibitors, ARBs) indicated for severe AR with symptoms, LV dysfunction, or LV dilatation, but not for long-term management of asymptomatic mild to moderate AR and normal LV function

FOLLOW-UP—asymptomatic mild AR with normal LV function and little/no LV dilatation can be followed annually with clinical exam and echocardiogram every 2–3 years (sooner if symptoms emerge). Asymptomatic severe AR with normal LV function and LV dilatation (>60 mm) should be seen every 6 months with echocardiogram every 2–3 years

PROCEDURES—intraaortic balloon pumps should be avoided

AORTIC VALVE REPLACEMENT (AVR)

- **RECOMMENDED INDICATIONS** (**CLASS I**)—if symptomatic severe AR; asymptomatic chronic severe AR (regurgitant fraction ≥50%, regurgitant volume ≥60 mL/beat, Doppler jet width ≥65% of LVOT) and LVEF <50%; or severe AR and undergoing cardiac surgery for other reasons
- **REASONABLE INDICATIONS** (**CLASS IIa**)—if asymptomatic severe AR with normal LVEF ≥50% but severe LV dilatation (LVESD >50 mm); or moderate AR and undergoing other cardiac surgery
- **POSSIBLE INDICATIONS** (**CLASS IIb**)—if asymptomatic severe AR and normal LVEF ≥50% but with progressive severe LV dilatation (LVEDD >65 mm) and low surgical risk

Mitral Stenosis

Circulation 2009 119:11
AHA/ACC Valvular Heart Disease 2014 Guidelines

DIFFERENTIAL DIAGNOSIS

RHEUMATIC HEART DISEASE
MITRAL ANNULAR CALCIFICATION
CONGENITAL
ENDOCARDITIS
ATRIAL MYXOMA
PROSTHETIC VALVE DYSFUNCTION
COR TRIATRIATUM

PATHOPHYSIOLOGY

STENOTIC MITRAL VALVE—left ventricular inlet obstruction → left atrial overload and left ventricle output failure → atrial fibrillation, pulmonary hypertension and eventually right heart failure

CLINICAL FEATURES

HISTORY—symptoms related to pulmonary hypertension (dyspnea, hemoptysis, chest pain), symptoms related to right heart failure (hepatomegaly, ascites, edema), hoarseness (Ortner's syndrome, due to enlarged left atrium compressing on recurrent laryngeal nerve), complications (endocarditis, thromboembolism), past medical history (rheumatic fever), medications

PHYSICAL

- **GENERAL APPEARANCE**—tachypnea, peripheral cyanosis, mitral facies (purple patches on cheeks secondary to vasoconstriction)
- **VITALS**—decreased pulse volume
- **JVP**—prominent a wave (pulmonary hypertension), absent a wave (atrial fibrillation), cv wave (tricuspid regurgitation)
- **CARDIAC**—right ventricular heave, palpable P2 (pulmonary hypertension), loud S1 (valve cusps widely apart at the onset of systole) in early disease, soft S1 in severe disease (valves rigid), loud S2, absent S3, opening snap (over apex and left lower sternal border; the earlier the opening snap, the more severe the stenosis), low pitch diastolic rumble (over

CLINICAL FEATURES (CONT'D)

apex, left decubitus position in expiration) ± pre-systolic accentuation, tricuspid regurgitation

- **ABDOMINAL**—hepatomegaly, ascites, edema

INVESTIGATIONS

BASIC

- **CXR**—left atrial enlargement, splaying of carina
- **ECHOCARDIOGRAM**—TEE to exclude left atrial thrombus before treatment
- **ECG**—P mitrale, RVH

SPECIAL

- **CARDIAC CATHETERIZATION**

DIAGNOSTIC AND PROGNOSTIC ISSUES

MITRAL STENOSIS AND SEVERITY

- **PROGRESSIVE**—mitral valve area (MVA) >1.5 cm^2, diastolic pressure half-time <150 ms
- **SEVERE**—MVA ≤1.5 cm^2 (MVA ≤1.0 cm^2 with very severe MS), diastolic pressure half-time ≥150 ms (diastolic pressure half-time ≥220 ms with very severe MS); associated with severe left atrial enlargement and pulmonary artery systolic pressure >30 mmHg. Note, transmitral mean gradient often >5–10 mmHg but mean pressure gradient varies greatly according to heart rate
- **SYMPTOMS**—often present when MVA ≤1.5 cm^2 (i.e., with severe MS). Onset of symptoms may be precipitated by exercise, emotional stress, infection, pregnancy, or rapid atrial fibrillation

PROGRESSION—approximately 0.1–0.3 cm^2/year. Initially slow stable course (latent period) of 20–40 years between rheumatic fever and symptoms. From onset of symptoms (accelerated period), around 10 years until disability. Overall 10-year survival is 50–60% in untreated symptomatic MS, >80% in asymptomatic. Median survival <3 years with severe pulmonary hypertension

MANAGEMENT

LIFESTYLE CHANGES—salt restriction/diuretics

MEDICATIONS—**negative chronotropic agents** and HR control to prolong diastolic filling (β-blockers, non-dihydropyridine calcium channel blockers). **Anticoagulation** for patients with concomitant atrial fibrillation (irrespective of $CHADS_2$ score), left atrial thrombus, or prior

MANAGEMENT (CONT'D)

embolic event (even if in sinus rhythm). **Prophylaxis for rheumatic fever** (secondary prevention)

FOLLOW-UP—any change in symptoms warrant reevaluation and echocardiogram. Otherwise, yearly evaluation in asymptomatic patients including CXR and ECG. Yearly echocardiogram for severe MS

PROCEDURES—indicated when symptomatic severe mitral stenosis. **Percutaneous balloon mitral valvuloplasty** (particularly for patients with non-calcified mitral valve, no left atrial thrombus, mild mitral regurgitation, and no other cardiac interventions) is equivalent to **surgical valvuloplasty** in terms of success. Average increase in valve area is 1.0 cm^2

SPECIFIC ENTITIES

ACUTE RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

- **PATHOPHYSIOLOGY**—group A *Streptococcus* infection → non-suppurative inflammation with cardiac, joints, and CNS manifestations 2–4 weeks later. Post-*Streptococcus* glomerulonephritis and scarlet fever may also occur separately as complications of group A *Streptococcus* infection
- **JONES CRITERIA FOR ACUTE RHEUMATIC FEVER**
  - **MAJOR CRITERIA ★J♥NES★**
    - **JOINT-MIGRATORY POLYARTHRITIS**
    - **♥CARDITIS** (pericarditis, myocarditis, valvulitis)
    - **NODULES** (subcutaneous)
    - **ERYTHEMA MARGINATUM**
    - **SYDENHAM CHOREA**
  - **MINOR CRITERIA**—clinical (fever, polyarthralgias), laboratory (↑ ESR, prolonged PR interval)
  - **DIAGNOSIS**—either two major criteria or one major criterion and two minor criteria, **plus** evidence of antecedent streptococcal infection (e.g., positive throat culture or rapid antigen detection test or elevated streptococcal antibody test)
- **INVESTIGATIONS**—anti-Streptolysin O antibodies, anti-DNase B, antihyaluronidase, positive throat culture, echocardiogram
- **TREATMENTS**—patients with rheumatic disease are at high risk of recurrent rheumatic fever. Recurrent disease causes additional valve damage, and thus these patients should receive **secondary prophylaxis** for rheumatic fever (*benzathine penicillin G* 1.2 M U IM

SPECIFIC ENTITIES (CONT'D)

q4weeks, *penicillin V* 250 mg PO BID, or *azithryomycin* 250 mg PO daily if allergic to penicillin). For patients with valvular involvement, therapy should continue for at least 10 years, or until age 40 (whichever is longer). With a history of carditis in the absence of persistent valvular disease, treat for 10 years, or until age 21 (whichever is longer)

Mitral Regurgitation AHA/ACC Valvular Heart Disease 2014 Guidelines

DIFFERENTIAL DIAGNOSIS

PRIMARY MR (VALVE ABNORMALITY)—rheumatic heart disease, infective endocarditis, mitral valve prolapse, myxomatous degeneration (Barlow's valve), fibroelastic deficiency disease, mitral annular calcification, ruptured chordae tendineae, drugs (fenfluramine)

SECONDARY MR (LEFT VENTRICULAR DILATATION)—myocardial infarction, dilated cardiomyopathy

PATHOPHYSIOLOGY

LEAKY MITRAL VALVE—left atrial and ventricle volume overload → atrial fibrillation and left heart failure

CLINICAL FEATURES

CLINICAL FEATURES—exertional dyspnea, fatigue, decreased S1, widely split S2, S3, holosystolic murmur (over apex), displaced and enlarged apex

INVESTIGATIONS

BASIC

- **CXR**—cardiomegaly, LAE
- **ECHOCARDIOGRAM**
- **ECG**—P mitrale, LVH

SPECIAL

- **CARDIAC CATHETERIZATION**

MANAGEMENT

MEDICATIONS—no specific therapy for MR. Treat concomitant atrial fibrillation if present

FOLLOW-UP—asymptomatic mild MR with normal LV function and no LV dilatation can be followed annually. Asymptomatic severe MR should be seen every 6–12 months with echocardiogram at the time of assessment

PROCEDURES—**mitral valve repair** (generally better outcome if technically possible) or **replacement** if symptomatic, atrial fibrillation, pulmonary hypertension, end-systolic dimension ≥40 mm, or LVEF 30–60%. Transcatheter mitral valve repair may be considered for severely symptomatic, severe primary MR with prohibitive surgical risk

MANAGEMENT (CONT'D)

SPECIFIC ENTITIES

TRICUSPID REGURGITATION

- **PATHOPHYSIOLOGY**—leaky tricuspid valve → right atrium and ventricle volume overload → eventually decompensation leading to right heart failure (hepatosplenomegaly, ascites, peripheral edema)
- **CAUSES**—right ventricular dilatation (left heart failure, pulmonary hypertension, Eisenmenger syndrome, pulmonic stenosis), valve abnormality (rheumatic heart disease, infective endocarditis, Ebstein's anomaly). Rarely is it due to isolated tricuspid valve abnormality
- **CLINICAL FEATURES**—cachexia, jaundice (congestive hepatomegaly), JVP cv wave, RV heave, S3 (with dilated RV), S4 (with stiff RV), holosystolic murmur (over left lower sternal border), edema
- **INVESTIGATIONS**—ECG (P pulmonale, RVH), CXR (cardiomegaly), echocardiogram, cardiac catheterization, rule out intracardiac shunts
- **TREATMENTS**—valve repair or replacement if severe symptoms

MITRAL VALVE PROLAPSE

- **PATHOPHYSIOLOGY**—prevalence 0.6–2.5% of population. May be sporadic or familial connective tissue disorder with morphologic abnormalities of the mitral valve (increased leaflet thickness and redundancy, chordal elongation, and sagging of the leaflets into the left atrium in systole)
- **TREATMENTS**—*ASA* 75–325 mg PO daily for history of transient ischemic attacks, atrial fibrillation (age <65 years, no MR, no HTN, no HF). Anticoagulation with warfarin for atrial fibrillation (if age >65, MR, HTN, or HF), history of stroke/TIA, or left atrial thrombus

SPECIFIC ENTITIES (CONT'D)

TWO SUBTYPES OF MITRAL VALUE PROLAPSE

	Mild subtype	Severe subtype
Demographics	Mainly women (age 20–50)	Mainly men (age 40–70)
Pathology	Mild leaflet abnormalities Minimal MR	Myxomatous disease Considerable leaflet thickening and MR
Symptoms	Orthostatic hypotension Palpitations	Atrial fibrillation
Physical findings	Mid-systolic click with or without a late systolic murmur	MR murmur Chordal rupture may lead to sudden worsening of MR
Prognosis	Few patients have progressive MR	Progressive MR requiring surgery Increased risk of sudden death

Endocarditis

ACC/AHA Infective Endocarditis 2008 Focused Update
AHA Infective Endocarditis 2005 Guidelines
NEJM 2001 345:18

DIFFERENTIAL DIAGNOSIS

INFECTIVE ENDOCARDITIS

- **COMMON**—*Streptococcus viridans* (*S. sanguis*, *S. mutans*, *S. mitis*), *Streptococcus pneumoniae*, *Streptococcus bovis*, *Enterococcus* (*E. faecalis*, *E. faecium*), *Staphylococcus aureus*, Gram-negative bacilli
- **LONG INCUBATION TIME (7–21) DAYS ★HACEK★**
  - ***H****aemophilus*
  - ***A****ctinobacillus*
  - ***C****ardiobacterium*
  - ***E****ikenella*
  - ***K****ingella*
- **SPECIAL MEDIA**—*Mycoplasma*, *Chlamydia*, *Legionella*, *Brucella*, *Bartonella*, *Coxiella burnetii* (Q fever), *Histoplasma*, *Tropheryma whippelii*

MARANTIC ENDOCARDITIS—non-bacterial thrombotic endocarditis secondary to malignancy (usually adenocarcinoma) or SLE (Libman–Sacks endocarditis)

PATHOPHYSIOLOGY

SUBTYPES—classified as acute vs. subacute, native valve vs. prosthetic valve, and right sided vs. left sided

- **NATIVE HEART VALVE**—usually *S. viridans*, *S. bovis*, enterococci
- **PROSTHETIC HEART VALVE**—<**2 months** (usually coagulase negative staphylococci, may need to treat surgically), >**1 year** (usually *S. viridans*, *S. bovis*, enterococci)
- **INJECTION DRUG USE**—usually *S. aureus* and Gram negative rods. Tricuspid valve most commonly affected

PATHOPHYSIOLOGY (CONT'D)

- **CANCER**—about 50% of patients with *S. bovis* endocarditis also have neoplasms of the GI tract

RISK FACTORS FOR ENDOCARDITIS

- **HIGH RISK**—complex cyanotic congenital heart disease (unrepaired or incompletely repaired cyanotic congenital heart disease, including palliative shunts and conduits; completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure; repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device), surgically constructed systemic pulmonary shunts, previous infective endocarditis, prosthetic heart valve, cardiac transplantation recipients who develop cardiac valvulopathy
- **MODERATE RISK**—most other congenital heart diseases, acquired valvular disease (rheumatic heart disease, mitral/aortic/pulmonary/tricuspid stenosis or regurgitation), mitral valve prolapse with valvular regurgitation or leaflet thickening, hypertrophic cardiomyopathy
- **LOW OR NO RISK**—secundum ASD or surgically repaired ASD, VSD, PDA, mitral valve prolapse with thin leaflets in the absence of regurgitation, ischemic heart disease, previous CABG
- **NON-CARDIAC**—IDU, poor dental hygiene, long-term hemodialysis, long-term indwelling catheter, procedures (GU, GI, surgical wound infection), diabetes, HIV

CLINICAL FEATURES

HISTORY—fever, murmur, dyspnea, chest pain, anorexia, weight loss, malaise, night sweats, complications (painful nodules, rash, stroke, myocardial infarction, any infections), past medical history (structural heart disease, recent procedures [dental, GI, GU], IDU, SLE, malignancy), medications

PHYSICAL—fever, splinter hemorrhages, clubbing, Osler nodes (tender, subcutaneous nodules in pulp of digits or thenar eminence), Janeway lesions (nontender, erythematous, hemorrhagic pustular lesions on palms or soles), needle track marks, petechiae over conjunctivae and oral mucosa, Roth spots (pale areas surrounded by hemorrhage on fundoscopic examination), lymphadenopathy, respiratory examination (HF), murmur (regurgitant), splenomegaly, petechiae over legs

HIGH INDEX OF SUSPICION—always consider endocarditis in the differential when dealing with fever of unknown origin, persistent bacteremia, HF, MI, myocarditis, pericarditis, stroke, pneumonia, pulmonary embolism, splenic infarction, glomerulonephritis, septic arthritis, and osteomyelitis. All patients with *S. aureus* bacteremia should undergo echocardiography (25% have IE)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, LDH, ESR, ANA, serology (HBV, HCV, HIV), urinalysis
- **MICROBIOLOGY**—blood C&S × 3 (endocarditis protocol and blood C&S × 2 daily until culture negative), sputum Gram stain/AFB/C&S, urine C&S, stool C&S, O&P, C. diff toxin A/B
- **IMAGING**—CXR, echocardiogram (TEE >TTE), CT chest/abd
- **ECG**—heart block

DIAGNOSTIC AND PROGNOSTIC ISSUES

MODIFIED DUKE'S CRITERIA

- **MAJOR**—positive blood culture × 2 (or positive blood culture × 1 for *C. burnetii*), echocardiographic evidence (oscillating intracardiac mass, abscess, new partial dehiscence of a prosthetic valve), new murmur
- **MINOR**—**fever** (>38 °C [100.4 °F]), **risk factor** (cardiac conditions, IDU), **vascular phenomena** (major arterial emboli, septic pulmonary infarct, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions), **immunologic phenomena** (glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor), **positive blood culture** not meeting major criteria
- **DIAGNOSIS**—likely endocarditis if 2 major, 1 major plus 2 minor, or 5 minor criteria

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

ECHOCARDIOGRAM—transesophageal echocardiogram (TEE sens 90–100%, spc 95–100%) preferred over transthoracic echocardiogram (TTE sens 50–80%, spc 90%) for detecting vegetations, perivalvular extension of infection and abscesses, diagnosing prosthetic valve endocarditis, and for differentiating between uncomplicated *Staphylococcus aureus* bacteremia and endocarditis

PROGNOSIS—mortality of 25–50% for prosthetic valve endocarditis, 35% for Staphylococcal endocarditis and 10% for Streptococcal endocarditis

Related Topics
Aortic Regurgitation (p. 56)
Mitral Regurgitation (p. 59)
Tricuspid Regurgitation (p. 59)

MANAGEMENT

EMPIRIC ANTIBIOTIC THERAPY—**native valve and non-IDU** (*ampicillin* 2 g IV q4h or *cloxacillin* 2 g IV q4h plus *gentamicin* 1 mg/kg IV q8h, or *vancomycin* 1 g IV q12h plus *gentamicin* 1 mg/kg IV q8h), **native valve and IDU** (*cloxacillin* 2 g IV q4h plus *gentamicin* 1 mg/kg IV q8h or *vancomycin* 1 g IV q12h plus *gentamicin* 1 mg/kg IV q8h), **prosthetic valve** (*vancomycin* 1 g IV q12h plus *gentamicin* 1 mg/kg IV q8h plus *rifampin* 600 mg PO daily)

TARGETED ANTIBIOTIC THERAPY (please refer to the Sanford Guide to Antimicrobial Therapy for up to date recommendations)—**Streptococci** (*penicillin G* 2–3MU IV q4h or *ceftriaxone* 2 g IV/IM q24h × 4 weeks. *Gentamicin* 1 mg/kg IV q24h × 2 weeks may be added in certain circumstances to shorten the course by 2 weeks). **Penicillin-sensitive Enterococci** (*ampicillin* 2 g IV q4h or *vancomycin* 1 g IV q12h × 4–6 weeks, plus *gentamicin* 1 mg/kg IV q8h × 4–6 weeks for native valve). **Penicillin-resistant Enterococci** (*vancomycin* 1 g IV q12h × 6 weeks, plus *gentamicin* 1 mg/kg IV q8h × 6 weeks for native valve). ***S. aureus*** (*cloxacillin* 2 g IV q6h or *nafcillin* or *oxacillin* 3 g IV q6h or *cefazolin* 2 g IV q8h × 2–6 weeks [depending on right- or left-sided valve] ± *gentamicin* 1 mg/kg IV q8h × 3–5 days: for native valve).

MANAGEMENT (CONT'D)

MRSA (*vancomycin* 1 g IV q12h×6 weeks for native valve). **HACEK** (*ceftriaxone* 2 g IV/IM q24h or *ampicillin-sulbactam* 3 g IV q6h or *ciprofloxacin* 500 mg PO BID×4 weeks). For prosthetic valve infection, therapy is usually longer (by 2–4 weeks) with gentamicin

SURGERY—valvular replacement (<10% reinfection rate. See indications below)

TREATMENT ISSUES

INDICATIONS FOR SURGERY—in the acute period, refractory congestive heart failure is the most important indication. Other indications include perivalvular extension of infection with abscess, fistula, or heart block; failure of antibiotic therapy with persistent bacteremia; infection with fungi or untreatable pathogens; Staphylococci on a prosthetic valve; or recurrent embolic events with persistent vegetation(s) despite appropriate antibiotic therapy. Consider early surgical consult for mobile vegetation(s) >10 mm with or without emboli

OVERALL RECOMMENDATIONS FOR ENDOCARDITIS PROPHYLAXIS—only given to patients with the highest risk of developing endocarditis, which include the following:

TREATMENT ISSUES (CONT'D)

- **HIGH-RISK CONDITIONS**—prosthetic valve, prosthetic material used for valve repair, unrepaired cyanotic congenital heart defect, repaired cyanotic congenital heart defect with residual defects at the site or adjacent to the site of the prosthetic device, completely repaired cyanotic congenital heart defect with prosthetic material or device during first 6 months after procedure, cardiac transplant recipients with valvulopathy, previous endocarditis
- **PROCEDURES**
  - **ORAL CAVITY**—dental procedures that involve manipulation of gingival or peripical region of teeth, perforation of oral mucosa
  - **RESPIRATORY TRACT**—tonsillectomy, adenoidectomy, bronchoscopy with a rigid bronchoscope, or flexible bronchoscopy if biopsied
  - **GI/GU TRACT**—prophylaxis generally not recommended
- **PROPHYLAXIS REGIMENS**—give one of the following 30–60 min prior to procedure: *amoxicillin* 2 g PO, *ampicillin* 2 g IM/IV, *cefazolin* 1 g IV/IM, *ceftriaxone* 1 g IV/IM, *cephalexin* 2 g PO, *clindamycin* 600 mg PO/IM/IV, *azithromycin* 500 mg PO, *clarithromycin* 500 mg PO

Peripheral Vascular Disease

NEJM 2007 356:12

ACCF/AHA Peripheral Artery Disease 2005 and 2013 Guidelines

DIFFERENTIAL DIAGNOSIS OF CLAUDICATION

ARTERIAL

- **ATHEROSCLEROSIS**
- **INTRALUMINAL OCCLUSION**—embolism, thrombosis, dissection, adventitial cystic disease, arterial fibrodysplasia, arterial tumor, occluded limb aneurysm
- **VASCULITIS**—Takayasu's arteritis, temporal arteritis, thromboangiitis obliterans
- **VASOSPASM**
- **DRUGS**—ergot
- **FIBROSIS**—iliac endofibrosis, radiation fibrosis, retroperitoneal fibrosis
- **TRAUMA**

VENOUS—DVT, thrombophlebitis, venous congestion

NEUROPATHIC—spinal stenosis, peripheral neuropathy

OTHERS—arthritis (hips, knees), compartment syndrome

CLINICAL FEATURES

HISTORY—pain, discomfort, or fatigue that occurs in leg muscle with exercise and improves with resting (ischemic intermittent claudication is NOT sensitive for peripheral vascular disease), maximum walking distance, non-healing wounds, trauma, DVT risk factors, past medical history (CAD, HF, AF, stroke, TIA, renal disease, hypertension, cholesterol), medications

PHYSICAL—comprehensive pulse examination of lower extremity

- **ANKLE BRACHIAL INDEX** (ABI)—abnormally high measurement >1.40 associated with noncompressible calcified vessel (and unreliable), 1.00–1.40 normal, 0.91–0.99 borderline, and ≤0.90 abnormal. If ≤0.90 significant narrowing of one or more blood vessels in the legs likely present, <0.8 intermittent claudication, <0.4 resting claudication, <0.25 critical limb ischemia. An ABI that ↓ by 20% following exercise

CLINICAL FEATURES (CONT'D)

is diagnostic of peripheral vascular disease, while a normal ABI following exercise eliminates the diagnosis

- **BUERGER'S TEST**—raise legs to 90° with patient in supine position. Check for return of rubor as the legs are lowered. Abnormal if angle of circulation <0° i.e., legs below table)
- **DEWEESE'S TEST**—disappearance of previously palpable distal pulses after walking exercise

VENOUS INSUFFICIENCY EXAMINATION—hemosiderin deposit, pitting edema, dermatitis, cellulitis, ulcer (with prominent granulation tissue over medial malleolus), superficial venous collaterals (DVT), varicose vein (palpate for tenderness or hardness that may suggest thrombophlebitis), Trendelenburg test (helps to determine whether venous reflux is related to the superficial or deep venous system. Occlude a collapsed superficial vein just below the site of suspected reflux from deep to superficial system. With patient standing, observe refilling of vein. Rapid refilling despite occlusion suggests incompetence of valves in the deep venous system, while slow refilling with occlusion and rapid refilling after occlusion is removed suggests incompetence of valves in the superficial venous system)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THE CLINICAL EXAMINATION PREDICT LOWER EXTREMITY PERIPHERAL ARTERIAL DISEASE?

	LR+	LR–
History		
Claudication	3.3	0.89
Inspection		
Wounds (ischemic ulcers and gangrene over lateral malleolus, tips of toes, metatarsal heads, bunion)	5.9	0.98
Discolouration	2.8	0.74
Atrophy	–	–
Absence of hair	–	–
Palpation		
Any palpable pulse abnormality (femoral, popliteal, posterior tibial, dorsalis pedis)	4.7	0.38
Coolness	5.9	0.92
Capillary refill time (firm pressure to planter aspect of great toe for 5 s. Abnormal if >5 s for normal skin)	1.9	–
Auscultation		
Any bruit (iliac, femoral, popliteal)	5.6	0.39

SPECIAL TESTS—**ankle brachial index** (ankle SBP by palpation/Doppler of posterior tibial or dorsalis pedis pulse divided by brachial SBP), **venous filling time** (raise leg to 45° for 1 min with patient supine position for vein to collapse. With patient then sitting up and legs dangling, determine the time for vein to refill. Abnormal if >20 s) (LR+ 3.6, LR– 0.8)

APPROACH—"for screening patients who require further testing to diagnose peripheral arterial disease, the most useful individual symptoms and signs are: claudication, femoral bruit and a pulse abnormality on palpation. The absence of claudication and the presence of normal pulses decrease the likelihood of moderate to severe disease. When considering patients who are symptomatic with leg complaints, the most useful individual findings are the presence of cool skin, the presence of at least 1 bruit and any palpable pulse abnormality. The absence of any bruit (iliac, femoral and popliteal) and the presence of normal peripheral pulses reduce the likelihood of peripheral arterial disease"

JAMA 2006 295:5

DISTINGUISHING FEATURES OF COMMON CAUSES OF LEG PAIN

	Claudication	Spinal stenosis	Venous congestion
Pain	Cramp, tiredness	Cramp, tiredness, tingling	Tightness, bursting
Sites	Buttock, hip, thigh, calf, foot	Buttock, hip, thigh	Groin, thigh
Worse	Walking	Walking, standing	Walking
Better	Rest	Sitting or change in position	Leg elevation
Others	Vascular dx, ↓ pulse	Lower back pain	History of DVT

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, urea, Cr, fasting glucose, fasting lipids, HbA1C
- **ANKLE BRACHIAL INDEX**—with or without exercise
- **DUPLEX ULTRASOUND**
- **ECG**

SPECIAL

- **CT/MR angiography**
- **ANGIOGRAPHY**

DIAGNOSTIC ISSUES

DIAGNOSTIC APPROACH—ABI <0.90 is sufficient for the diagnosis of peripheral arterial disease as it suggests >50% stenosis of peripheral vasculature (sens 90%, spc 98%). Patients with large vessel disease (distal aorta or iliac arteries) may only have abnormal ABI after exercise. Patients with non-compressible vessels (as suggested by ABI >1.30–1.40) should have toe-brachial index done. Perform duplex US or CT/MR angiogram if the diagnosis is uncertain or if revascularization is being considered. Digital-subtraction angiograph remains the gold standard

MANAGEMENT

RISK REDUCTION ★ABCDEFG★

- **ASA**
- **BLOOD PRESSURE CONTROL** (see HYPERTENSION p. 65)
- **CHOLESTEROL CONTROL** (see DYSLIPIDEMIA p. 70)
- **DIABETIC CONTROL** (see DIABETES p. 381)
- **EXERCISE** (30 min of moderate-intensity exercise 3–4×/week)
- **FAT REDUCTION** (see OBESITY ISSUES p. 457)
- **GET GOING TO QUIT SMOKING**! (see SMOKING ISSUES p. 480)

MEDICAL—antiplatelet (*ASA* 75–325 mg PO daily, *clopidogrel* 75 mg PO daily), high-intensity **statin** (*atorvastatin* 80 mg PO daily, *rosuvastatin* 40 mg PO daily). Consider *cilostazol* 100 mg PO BID for life-limiting claudication (in the absence of heart failure), but treatment with *pentoxifylline* 400 mg PO TID is of dubious benefit

SURGICAL—revascularization (surgery or percutaneous transluminal angioplasty)

TREATMENT ISSUES

REVASCULARIZATION—indicated for patients with significant functional limitations (lifestyle or jobs) despite maximal lifestyle and medical treatment. Not optimal for patients <40 with atherosclerosis obliterans, with non-disabling symptoms, diabetes, significant coronary risk factors, or other diseases associated with high mortality

SPECIFIC ENTITIES

VASCULAR DISEASE FAMILY—CAD, CVD, PVD, AAA, renal artery stenosis, chronic mesenteric ischemia

ABDOMINAL AORTIC ANEURYSM—U.S. Preventative Services Task Force recommends one-time screening with abdominal US for men 65–75 who have ever smoked. Repair is controversial for 4–5 cm [1.6–2 in.]; >5 cm [>2 in.] warrants surgical intervention (risk of spontaneous rupture is 22%/year). Monitor lesions ≤5 cm [≤2 in.] with ultrasound regularly (every 6 months if lesions 4 cm [1.6 in.], more frequent for bigger lesions). Operative mortality is 4–6% for elective repair, 19% for urgent repair, and 50% for repair of a ruptured aneurysm. No driving if AAA >6 cm [2.4 in.] in men, >5.5 cm [2.2 in.] in women

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE ABDOMINAL AORTIC ANEURYSM?

PALPATION—to detect abnormal widening of the aortic pulsation (sens 50% for AAA 4–4.9 cm [1.6–1.9 in.], sens 76% for AAA ≥5 cm [≥2 in.], LR+ 12 and LR– 0.72 for AAA ≥3 cm [≥1.2 in.], LR+ 15.6 and LR– 0.51 for AAA ≥4 cm [≥1.6 in.])

APPROACH—"abdominal palpation will detect most AAAs large enough to warrant surgery, but it cannot be relied on to exclude the diagnosis. The sensitivity of palpation appears to be reduced by abdominal obesity. When a ruptured AAA is suspected, imaging studies such as ultrasound or computed tomography should be performed regardless of physical findings"

UPDATE—sensitivity for palpation of AAA improved among thinner patients, especially if abdominal girth is <100 cm

JAMA 1999 281:1
The Rational Clinical Examination. McGraw-Hill, 2009

Hypertension

CHEP Hypertension 2014 Guidelines
JNC8 Hypertension 2014 Guidelines
JNC7 Hypertension 2003 Guidelines
NEJM 2003 348:7; NEJM 2006 355:4; NEJM 2007 357:8

DIFFERENTIAL DIAGNOSIS

★0–1–2–3-4★

0 **ESSENTIAL HYPERTENSION**
1 **ANATOMIC**—aorta (coarctation, aortic dissection)
2 **RENAL**—renal parenchymal disease (chronic renal failure, polycystic kidney disease), renal artery stenosis
3 **ADRENAL**—pheochromocytoma, Conn's syndrome, Cushing's syndrome
4 **SCENTS**
- **SUPER GROWTH**—acromegaly
- **CALCIUM**—hypercalcemia (hyperparathyroidism)
- **ESTROGEN OR OTHER DRUGS**—NSAIDs, corticosteroids, anabolic steroids, oral contraceptives, cocaine, amphetamines, MAO inhibitors, SNRIs, SSRIs, erythropoietin, cyclosporine, tacrolimus, midodrine, alcohol excess, licorice root
- **NEUROLOGIC**—Cushing's triad (hypertension, bradycardia, and respiratory depression associated with increased intracranial pressure)
- **THYROID**—hyperthyroidism, hypothyroidism
- **SLEEP APNEA**

PATHOPHYSIOLOGY

CLASSIFICATION OF HYPERTENSION

- **NORMAL**—SBP <120 mmHg *and* DBP <80 mmHg
- "**PREHYPERTENSION**"—SBP 120–139 mmHg *or* DBP 80–89 mmHg
- **STAGE 1 HYPERTENSION**—SBP 140–159 mmHg *or* DBP 90–99 mmHg
- **STAGE 2 HYPERTENSION**—SBP ≥160 mmHg *or* DBP ≥100 mmHg
- **MASKED HYPERTENSION**—BP consistently elevated with out-of-office measurements, but normotensive when measured in office; associated with ↑ cardiovascular risk
- **WHITE COAT HYPERTENSION**—BP consistently elevated with office measurements, but normotensive when out-of-office; possible slight ↑ cardiovascular risk (but still less than in masked or sustained hypertension)

PATHOPHYSIOLOGY (CONT'D)

- **HYPERTENSIVE EMERGENCY**—severe hypertension (usually SBP ≥220 and/or DBP ≥120 mmHg) with end organ damage such as pulmonary edema, aortic dissection, myocardial infarction, cerebrovascular hemorrhage, papilledema, fundoscopic hemorrhages or exudates, acute renal failure, eclampsia of pregnancy, and hypertensive encephalopathy
- **HYPERTENSIVE URGENCY**—severe hypertension (usually SBP ≥220 and/or DBP ≥120 mmHg) without findings of hypertensive emergency

ISOLATED SYSTOLIC HYPERTENSION—younger people tend to have isolated diastolic hypertension (50–60% of patients under 40). With age, large arteries tend to stiffen with decreased elasticity secondary to a combination of atherosclerosis, calcification, and elastin degradation. Thus, isolated systolic hypertension predominates with age (over 90% of patients over 70)

HYPERTENSIVE END ORGAN DAMAGE—ischemic heart disease, peripheral arterial disease, left ventricular hypertrophy, stroke, TIA, microalbuminuria or proteinuria, and chronic kidney disease

HYPERTENSIVE RETINOPATHY

- **MILD**—**focal arteriolar narrowing** (vasospasm), **generalized arteriolar narrowing** (increased vascular tone due to autoregulation, mild intimal hyperplasia, and hyaline degeneration in sclerotic stage). Subsequently, **arteriovenous nicking** (venous compression by a thickened arteriole, leading to dilation of vein around intersection) and **opacity of arteriolar wall** (widening and accentuation of the central light reflex leading to so-called copper wiring appearance)
- **MODERATE**—**hemorrhages** (blot, dot, or flame shaped due to disruption of the blood–retina barrier), **microaneurysms** (necrosis of the smooth muscles and endothelial cells), **hard exudates** (exudation of blood and lipids), and **soft exudates** (cotton wool spots, retinal ischemia)
- **MALIGNANT**—signs of moderate retinopathy plus swelling of the optic disc
- **UTILITY**—the retina provides a window of cerebral circulation. Risk of stroke (and death) increases with degree of retinopathy. Note that the stages may not be sequential

CLINICAL FEATURES

HISTORY—blood pressure levels, ambulatory/home monitoring, complications and hypertensive end organ damage, other cardiac risk factors (smoking, diabetes, dyslipidemia, obesity), past medical history (thyroid, renal, or adrenal disorders), medications (antihypertensives, steroids, illicit drugs)

PHYSICAL—vitals (heart rate, blood pressure), obesity (sleep apnea), moon facies and thoracocervical fat pad (Cushing's), low-pitched voice and acral enlargement (acromegaly), upper body better developed and continuous murmur over precordium/back (coarctation), narrowed oropharynx and ↑ neck circumference (OSA), goiter (hyperthyroidism), aortic regurgitation (aortic dissection), striae, renal bruits (renal artery stenosis), abdominal masses (polycystic kidney disease, adrenal tumors), radiofemoral delay and weak femoral pulses (coarctation). Assess complications including retinopathy, stroke, HF, AAA, and PVD

MEASURING BLOOD PRESSURE—NEJM 2009 360:e6

INVESTIGATIONS

BASIC

- **LABS**—lytes, urea, creatinine, fasting glucose, HbA1C, fasting lipid profile, urinalysis, urine microalbumin
- **24-H AMBULATORY BLOOD PRESSURE MONITOR**
- **ECG**

SECONDARY CAUSES WORKUP

- **HYPERALDOSTERONISM WORKUP**—if clinical features present (i.e., spontaneous hypokalemia <3.5 mmol/L; diuretic-induced hypokalemia <3.0 mmol/L; resistance to ≥3 antihypertensive drugs; adrenal incidentaloma with hypertension) then consider serum renin/aldosterone, saline infusion test, oral sodium loading test, adrenal vein sampling. Plasma renin activity is difficult to interpret in patients taking mineralocorticoid receptor antagonists (e.g., spironolactone)
- **PHEOCHROMOCYTOMA WORKUP**—if clinical features present (i.e., paroxysmal and/or severe hypertension refractory to usual antihypertensive drugs; symptoms of catecholamine excess; hypertension triggered by β-blockers, MAO inhibitors, micturition, or Valsalva maneuver; adrenal incidentaloma with hypertension; genetic syndrome [MEN2A, MEN2B, von Hippel-Lindau, neurofibromatosis]) then consider 24-h urine metanephrine, plasma fractionated metanephrines
- **OTHER ENDOCRINE WORKUP** (guided by clinical suspicion)—Ca, albumin, PTH, TSH, free T4, 24-h urine cortisol, 1 mg dexamethasone suppression test, late night salivary cortisol, IGF-1
- **RENOVASCULAR WORKUP**—if ≥2 clinical features present (i.e., sudden-onset or worsening hypertension and age >55 or <30 years; presence of abdominal bruit; resistance to ≥3 antihypertensive drugs; ↑ serum Cr ≥30% with ACEi or ARB; other atherosclerotic disease; or recurrent flash pulmonary edema), then consider renal Doppler US, CT/MR angiogram, renal angiogram
- **SLEEP OXIMETRY TEST**—if suspect sleep apnea

DIAGNOSTIC ISSUES

CLINICAL DIAGNOSIS OF HYPERTENSION

1. **Hypertensive urgency or emergency during first visit**?
   - Yes → hypertension diagnosed
   - No → proceed to step 2
2. **What is the blood pressure during initial visit**?
   - SBP ≥180 mmHg and/or DBP ≥110 mmHg → repeat BP at least 2 more times at the same visit (discard first reading and average latter 2 readings). If mean BP 180/110 or greater, diagnosis of hypertension is confirmed
   - SBP 140–179 mmHg and/or DBP 90–109 mmHg (or mean automated office BP taken using an automated device that performs multiple readings with the patient alone in the room is SBP 135–179 and/or DBP 85–109 mmHg), then obtain out-of-office readings before second visit
   - SBP 130–139 and/or DBP 85–89 mmHg → annual follow-up
3. **Out-of-office readings can be measured using 24-hour ambulatory monitoring (ABPM) or a home BP series (HBPM).** ABPM is preferred. Further information on how to perform these can be found at www.hypertension.ca
4. **What is the average blood pressure from the ambulatory BP monitor**?
   - Mean awake SBP ≥135 mmHg or DBP ≥85 mmHg → hypertension diagnosed

DIAGNOSTIC ISSUES (CONT'D)

- Mean awake SBP <135 mmHg and DBP <85 mmHg → long-term follow-up
- Mean 24-h SBP ≥130 mmHg or DBP ≥80 mmHg → hypertension diagnosed
- Mean 24-h SBP <130 mmHg or DBP <80 mmHg → long-term follow-up

5. **What is the average blood pressure from home BP monitoring**?
   - Average SBP ≥135 or DBP ≥85 mmHg → hypertension diagnosed
   - Average SBP <135 or DBP <85 mmHg → repeat home BP monitoring (to confirm average BP <135/85 mmHg), or consider ambulatory BP monitoring (step 8), then long-term follow-up

CHEP Hypertension 2015 Guidelines
http://www.hypertension.ca

ACUTE MANAGEMENT

ACUTE—ABC, O_2, IV

HYPERTENSIVE EMERGENCY—*labetalol* 20 mg IV bolus initially, then 20–80 mg q10min, or 2 mg/min IV infusion (loading) then 2–8 mg/min, maximum total dose of 300 mg. *Nitroprusside* 0.25–0.5 μg/kg/min IV initially, increase by 0.5 μg/kg/min increments, to usually target 3 μg/kg/min (rarely >4 μg/kg/min, maximum 10 μg/kg/min). *Nicardipine* 5 mg/h IV initially, titrate to a maximum of 15 mg/h. *Fenoldopam* 0.1 μg/kg/min IV initially, titrate dose q15min. Consider ICU admission. Workup and treatment of underlying causes once stabilized

HYPERTENSIVE URGENCY—*furosemide* 20–40 mg PO/IV × 1 dose. *Clonidine* 0.1–0.3 mg PO BID. *Captopril* 25–50 mg PO TID. *Labetalol* 5–20 mg IV q15min or *hydralazine* 5–20 mg IV q15min to keep SBP <170 mmHg. Lower BP over hours to days, 25–30% lower than baseline; avoid lowering BP too rapidly (risk of stroke and MI if BP dropped to below minimum level required to maintain tissue perfusion). Workup and treatment of underlying cause once stabilized

LONG-TERM MANAGEMENT

LIFESTYLE CHANGES—**healthy diet** (high in fresh fruits, vegetables, and low fat dairy products; low in saturated fat and salt <100 mmol/day). **Physical activity** (optimum 30–60 min of moderate cardiopulmonary activity 4–7×/week). **Reduction in alcohol** (<2 drinks/day in men and <1 drink/day in women). **Weight loss** (in those with BMI >25 kg/m^2, lose >5 kg). **Smoke free environment**

ANTIHYPERTENSIVES ★ABCD★

- **ACE INHIBITOR**—*ramipril* 2.5–10 mg PO daily-BID, *captopril* 12.5–50 mg PO TID, *perindopril* 2–8 mg PO daily, *lisinopril* 2.5–10 mg PO daily, *trandolapril* 1–8 mg PO daily
- **ARB**—*candesartan* 8–32 mg PO daily, *losartan* 50–100 mg PO daily, *irbesartan* 150–300 mg PO daily, *valsartan* 80–320 mg PO daily
- **β-BLOCKERS**—not recommended as first-line agent for uncomplicated hypertension in those ≥60-years old. *Metoprolol tartrate* 50–100 mg PO BID, *atenolol* 50–100 mg PO daily, *labetalol* 100–400 mg PO TID, *bisoprolol* 5–10 mg PO daily
- **CALCIUM CHANNEL BLOCKERS**—*amlodipine* 2.5–10 mg PO daily, *diltiazem CD* 180–360 mg PO daily
- **DIURETICS**—*chlorthalidone* 12.5–25 mg PO daily, *indapamide* 1.25–2.5 mg PO daily, *hydrochlorothiazide* 12.5–25 mg PO daily, *spironolactone* 12.5–50 mg PO daily
- **α1 BLOCKERS**—*terazosin* 1–20 mg PO daily, *doxazosin* 1–16 mg PO daily
- **α1 AGONIST**—*clonidine* 0.1–0.5 mg PO BID
- **OTHERS**—minoxidil, phentolamine, hydralazine

TREAT UNDERLYING CAUSE

TREATMENT ISSUES

ACE INHIBITORS/ANGIOTENSIN RECEPTOR BLOCKERS

- **INDICATIONS**—HF, post-MI, diabetes, proteinuria, renal failure (with caution), LVH
- **CONTRAINDICATIONS**—pregnancy, ESRD, bilateral RAS
- **ADVERSE EFFECTS**—cough (with ACE inhibitor), angioedema, hyperkalemia

β-BLOCKERS

- **INDICATIONS**—resting tachycardia, HF, migraine, glaucoma, CAD/post-MI
- **CONTRAINDICATIONS**—asthma, severe PVD, Raynaud's phenomenon, depression, bradycardia, second or third degree heart block and hypoglycemia-prone diabetics
- **ADVERSE EFFECTS**—depression, ↓ exercise tolerance, bradycardia, hypotension

TREATMENT ISSUES (CONT'D)

CALCIUM CHANNEL BLOCKERS

- **DIHYDROPYRIDINE** (potent vasodilators)—nifedipine, amlodipine, felodipine, nicardipine
- **NON-DIHYDROPYRIDINE** (heart rate control)—verapamil (cardiac depressant activity), diltiazem (some cardiac depressant, some vasodilator)
- **INDICATIONS**—angina pectoris, recurrent SVT (verapamil), Raynaud's phenomenon (dihydropyridine), migraine, heart failure due to diastolic dysfunction, esophageal spasm
- **CONTRAINDICATIONS**—second or third degree heart block (non-dihydropyridine), HF with moderate to marked systolic dysfunction
- **ADVERSE EFFECTS**—nifedipine (dizziness, headache, flushing, and peripheral edema), verapamil (↓ cardiac contractility, conduction, and constipation), diltiazem (both side effects but a lot less severe)

DIURETICS

- **INDICATIONS**—most patients (particularly those of African descent)
- **CONTRAINDICATIONS**—allergy
- **ADVERSE EFFECTS**—↓ K, ↑ Ca (thiazides), hyperuricemia, ↑ cholesterol, ↑ glucose, ↑ insulin resistance, impotence

TREATMENT ISSUES (CONT'D)

BLOOD PRESSURE TREATMENT TRIGGERS AND TARGETS

	Blood pressure (mmHg)
When to start therapy?	
No macrovascular target organ damage or other independent cardiovascular risk factors	≥160/100
Macrovascular target organ damage or other independent cardiovascular risk factors	≥140/90
Very elderly	≥160
What should the targets be?	
Diabetes	<130/80
All others (including non-diabetic chronic kidney disease)	<140/90
Very elderly (≥80-years old)	<150 (systolic)

CHEP Hypertension 2014 Guidelines
http://www.hypertension.ca

OVERALL APPROACH TO CHOICE OF THERAPY

Condition	**Drug of Choice**
HTN without other indications	A/B/C/D → AC/AD/BC/BD → ABC/ACD/BCD/ABD → ABCD Avoid B as first line if age ≥60 ACEi may be less effective in those of African descent
Isolated systolic hypertension	ARB/C1/D → ARB plus either C1 or D → ARB plus C1 plus D Avoid B
Angina	ACEi/B → ACEi plus B → add C1
Prior myocardial infarction	AB → ABC
Heart failure	AB → ABD (including spironolactone) → ACEi/ARB/B/D. Avoid hydralazine and minoxidil if LVH
Prior cerebrovascular disease	AD → add other agents
Peripheral vascular disease	A/B/C/D plus ASA. Avoid B if severe PVD
Diabetes without nephropathy	A/C1/D → AC1/AD → add B or C2
Diabetes with nephropathy	A → AC/AB/AD
CKD ± proteinuria	A → AD → add other agents
Asthma	A/C/D. Avoid B
BPH	α-blockers
Migraine	B
Thyrotoxicosis	B
Essential tremor	B
Postural hypotension	Avoid vasodilators and diuretics
Raynaud's	C (dihydropyridine)

TREATMENT ISSUES (CONT'D)

Condition	Drug of Choice
Gout	Avoid D
Hyperkalemia	C/D. Avoid aldosterone antagonists
Hyponatremia	A/B/C. Avoid D
Pregnancy	Labetalol/methyldopa/nifedipine. Avoid ACE inhibitors and ARB (teratogenic)

where *A* ACE inhibitors/ARBs, *B* β-blockers, *C* calcium channel blockers, *C1* long-acting dihydropyridine CCB, *C2* non-dihydropyridine CCB, *D* diuretics

SPECIFIC ENTITIES

RENAL ARTERY STENOSIS (RAS)

- **PATHOPHYSIOLOGY**—causes include atherosclerosis and fibromuscular dysplasia
- **CLINICAL FEATURES**—systemic atherosclerosis, uncontrolled hypertension, flash pulmonary edema, asymmetrical kidneys, renal failure with ACE inhibitor, and renal bruits
- **DIAGNOSIS**—MR angiogram (preferred as noninvasive and high sensitivity/specificity), CT angiogram (anatomical information), duplex US (anatomic and functional information), captopril-enhanced radioisotope renogram (functional information), contrast angiogram (gold standard)
- **TREATMENTS**—**medical** (cornerstone of management of atherosclerotic disease; risk factor reduction with blood pressure control [avoidance of ACE inhibitors/ARBs in *severe bilateral* renal artery stenosis], statin therapy, and antiplatelet agent), **angioplasty** (*not routinely recommended* for atherosclerotic disease because outcomes similar to medical therapy alone; consider if fibromuscular dysplasia, severe or refractory hypertension, recurrent flash pulmonary edema, or acute decline in renal function due to renal artery stenosis. Unlikely to restore renal function if small kidneys or high creatinine >300 μmol/L [3.4 mg/dL]), **surgery**

NEJM 2001 344:6
NEJM 2009 361:20
NEJM 2014 370:1

DIFFERENTIAL DIAGNOSIS OF ABDOMINAL BRUITS

- **CARDIOVASCULAR**—abdominal aortic aneurysm, aortocaval fistula
- **RENAL VASCULAR**—renal artery stenosis
- **GI VASCULAR**—celiac artery compression syndrome, mesenteric ischemia
- **HEPATIC VASCULAR**—cirrhosis, hepatoma, AV malformation, arterioportal fistula, Cruveilhier–Baumgarten sign (cirrhosis, portal hypertension, and caput medusa)

SPECIFIC ENTITIES (CONT'D)

- **SPLENIC VASCULAR**—splenic AV fistula, splenic artery dissection, splenic enlargement
- **PANCREATIC VASCULAR**—pancreatic carcinoma

RATIONAL CLINICAL EXAMINATION SERIES: IS LISTENING FOR ABDOMINAL BRUITS USEFUL IN THE EVALUATION OF RENOVASCULAR HYPERTENSION?

	LR+	LR–
Systolic and diastolic abdominal bruit	39	0.6
Any epigastric or flank bruit, including isolated systolic bruit	6.4	0.4
Systolic bruit	*4.3*	*0.5*
History of atherosclerotic disease	*2.2*	*0.5*

APPROACH—"given the high prevalence (7–31%) of innocent abdominal bruits in the younger age groups, it is recommended that if a systolic abdominal bruit is detected in a young, normotensive, asymptomatic individual, no further investigations are warranted. In view of the low sensitivity, the absence of a systolic bruit is not sufficient to exclude the diagnosis of renovascular hypertension. In view of the high specificity, the presence of a systolic bruit (in particular a systolic–diastolic bruit) in a hypertensive patient is suggestive of renovascular hypertension. In view of the lack of evidence to support characterizing bruits as to pitch, intensity and location, bruits should be reported only as systolic or systolic/diastolic"

JAMA 1995 274:16
The Rational Clinical Examination. McGraw-Hill, 2009

Related Topics
Aortic Dissection (p. 27)
Hyperaldosteronism (p. 398)
Pheochromocytoma (p. 398)

Hyperlipidemia

ACC/AHA 2013 Cholesterol Guidelines
Canadian Cardiovascular Society 2012 Dyslipidemia Guidelines

DIFFERENTIAL DIAGNOSIS OF HYPERCHOLESTEROLEMIA

PRIMARY—polygenic, familial hypercholesterolemia (IIa; suspect when total cholesterol >6 mmol/L [>232 mg/dL], LDL >5 mmol/L [>193 mg/dL]), sitosterolemia
SECONDARY—obesity, diabetes, hypothyroidism, nephrotic syndrome, medications (thiazides), cholestatic liver disease (primary biliary cirrhosis)

DIFFERENTIAL DIAGNOSIS OF HYPERTRIGLYCERIDEMIA

PRIMARY—dietary, familial hypertriglyceridemia (IV; suspect when TGL >5 mmol/L [>440 mg/dL]), LPL deficiency (I), dysbetalipoproteinemia (III), ApoCII deficiency
SECONDARY—obesity, diabetes, nephrotic syndrome, hypothyroidism, alcoholism, drugs (estrogen, tamoxifen, β-blockers, glucocorticoids, cyclosporine, glucocorticoids, novel antipsychotics, protease inhibitors, isotretinoin)

DIFFERENTIAL DIAGNOSIS OF COMBINED HYPERCHOLESTEROLEMIA AND HYPERTRIGLYCERIDEMIA

PRIMARY—familial combined hyperlipidemia (IIb), mixed hypertriglyceridemia (V), dysbetalipoproteinemia (III)
SECONDARY—diabetes, nephrotic syndrome, hypothyroidism, drugs (glucocorticoids, immunosuppressives, protease inhibitors), lipodystrophies

DIFFERENTIAL DIAGNOSIS OF LOW HDL

PRIMARY—familial hypoalphalipoproteinemia, Tangiers disease, ApoAI mutation, LCAT deficiency
SECONDARY—drugs (anabolic steroids, isotretinoin)

CLINICAL FEATURES

HISTORY—past medical history (diabetes, CAD, HF, stroke, TIA, renal disease, hypertension, liver disease, gallstones, hypothyroidism, HIV), medications

- **HYPERTRIGLYCERIDEMIA**—pancreatitis, chylomicronemia syndrome (dyspnea, confusion), hyponatremia, transaminitis, milky plasma (with blood work)
- **HYPERCHOLESTEROLEMIA**—premature atherosclerosis, aortic sclerosis/stenosis

PHYSICAL

- **HYPERTRIGLYCERIDEMIA**—lipemia retinalis (when TGL ≥22.6 mmol/L), eruptive xanthomas (commonly on buttocks, extensor surfaces of arms, back; when TG 11.3-22.6 mmol/L), hepatosplenomegaly
- **HYPERCHOLESTEROLEMIA**—tendon xanthomas (most commonly in Achilles tendon and extensor surfaces of hands), xanthelasmas, tuberous xanthomas (over areas susceptible to trauma), corneal arcus (premature when <40-years of age)

INVESTIGATIONS

BASIC

- **LABS**—total chol, TGL, LDL, HDL, apoB, Lp(a), fasting glucose, HbA1C, Cr, TSH, hsCRP, CK, AST, ALT, ALP, bilirubin, LDH

MANAGEMENT

LIFESTYLE CHANGES—**diet** (↑ fruit and vegetable intake, ↑ mono- and polyunsaturated fats, ↓ saturated fats and trans-fatty acid to <7% of calories, ↑ omega-3 fatty acid from fish and plant sources, *salmon oil* 3–9 g can ↓TGL). **Exercise**, **smoking avoidance**

MEDICATIONS

- **HMG-CoA REDUCTASE INHIBITORS** (↓↓ LDL ↑ HDL, ↓ TGL)—*atorvastatin* 10–80 mg PO daily, *rosuvastatin* 5–40 mg PO daily, *simvastatin* 10–80 mg PO daily, *pravastatin* 10–40 mg PO daily. Main side effects include myalgias, myopathy, and transaminitis
- **NPC1L1 TRANSPORTER INHIBITOR** (↓ LDL)—*ezetimibe* 10 mg PO daily
- **FIBRATES** (↓ LDL ↑ HDL, ↓↓ TGL)—*fenofibrate nanocrystallized tablet* [Lipidil EZ] 145 mg PO daily without regard to meals (best oral absorption), *fenofibrate micronized tablet* [Lipidil Supra] 160–200 mg PO with dinner (moderate oral absorption and modestly improved with food), *fenofibrate micronized capsule* [Lipidil Micro] 200 mg PO with dinner (poor oral absorption but improved with food), *gemfibrozil* 600 mg PO daily (safe in pregnancy beginning in second trimester). Main side effects include rash, pruritis, GI upset, gallstones, and myalgia

MANAGEMENT (CONT'D)

- **BILE-ACID SEQUESTRANTS** (↓ LDL, ↑ cholesterol synthesis)—*cholestyramine* 2–24 g PO daily, *colestipol* 5–30 g PO daily in divided doses. Main side effects include constipation, vitamin K deficiency, and drug interactions (bind to other drugs and prevent absorption)
- **NIACIN** (↓ TGL, ↓ LDL, ↑↑ HDL)—*nicotinic acid* 1–3 g PO daily. Main side effects include ↑ blood sugar, flushing (treat with ASA), hepatotoxicity, and gastric irritation
- **OMEGA-3 FATTY ACIDS** (↓ TGL, ↑ LDL)—*eicosapentaenoic acid/docosahexaenoic acid (EPA/DHA)* 3–4 g PO daily. Main side effects include ↑ blood sugar; flushing, hepatotoxicity, and gastric irritation
- **PCSK9 INHIBITOR** (↓↓↓ LDL)—*evolocumab*. Inhibits PCSK9 from binding to LDL receptor on hepatocytes, thus facilitating removal of LDL from circulation. Approved and possibly on market by 2016
- **ASPIRIN**—*ASA* 81 mg PO daily for secondary prevention

TREAT SECONDARY CAUSES/METABOLIC SYNDROME IF PRESENT

TREATMENT ISSUES

RISK CATEGORIES

- **HIGH**—10-year risk of cardiovascular event ≥20%, as estimated using validated risk calculator (Framingham Risk Score, Reynolds Risk Score); clinical vascular disease (e.g., CAD, CVA, TIA, PVD); abdominal aortic aneurysm; diabetes and age ≥40 years or >15 years duration and age ≥30 years or presence of microvascular disease; chronic kidney disease; high-risk hypertension. All high risk patients require treatment
- **MODERATE**—10-year risk of cardiovascular event 10–19%. Consider initiating treatment if LDL ≥3.5 mmol/L [135 mg/dL]; or LDL <3.5 mmol/L [135 mg/dL] *and* ApoB ≥1.2 g/L [120 mg/dL]; or LDL <3.5 mmol/L [135 mg/dL] *and* non-HDL-C ≥ 4.3 mmol/L [166 mg/dL]; LDL <3.5 mmol/L [135 mg/dL] *and* hsCRP >2 mg/L in men age >50 or women age >60
- **LOW**—10-year risk of cardiovascular event <10%. Consider initiating treatment if LDL ≥5.0 mmol/L [≥193 mg/dL]

TREATMENT ISSUES (CONT'D)

HYPERCHOLESTEROLEMIA

- **AMERICAN TREATMENT GUIDELINES**—treat according to severity of cardiovascular risk with appropriate intensity of statin irrespective of actual lipid levels achieved

INTENSITY OF STATIN THERAPY (ACC/AHA 2013 Guidelines)

High-intensity	Moderate-intensity	Low-intensity
↓ LDL-C by approximately ≥50%	↓ LDL-C by approximately 30 to <50%	↓ LDL-C by approximately <30%
Atorvastatin 40–80 mg PO daily	Atorvastatin 10–20 mg PO daily	Simvastatin 10 mg PO daily
Rosuvastatin 20–40 mg PO daily	Rosuvastatin 5–10 mg PO daily	Pravastatin 10–20 mg PO daily
	Simvastatin 20–40 mg PO daily	Lovastatin 20 mg PO daily
	Pravastatin 40–80 mg PO daily	Fluvastatin 20–40 mg PO daily
	Lovastatin 40 mg PO daily	
	Fluvastatin XL 80 mg PO daily	
	Fluvastatin 40 mg PO BID	

- **CANADIAN TREATMENT GUIDELINES**—"treat to target" with specific lipid levels as goal of therapy

TREATMENT TARGETS BASED ON RISK CATEGORY (CCS 2012 Guidelines)

	High risk	Moderate risk	Low risk
LDL	≤2 mmol/L [≤77 mg/dL] or ≥50% ↓ LDL	≤2 mmol/L [≤77 mg/dL] or ≥50% ↓ LDL	≥50% ↓ LDL
ApoB	≤0.80 g/L [<80 mg/dL]	≤0.80 g/L [≤80 mg/dL]	
non-HDL-C	≤2.6 mmol/L [≤100 mg/dL]	≤2.6 mmol/L [≤100 mg/dL]	

TREATMENT ISSUES (CONT'D)

HYPERTRIGLYCERIDEMIA

- **TREATMENT**—dietary modification (with reduced fat, simple sugars, and calories) and alcohol abstinence. Severe cases (TG >11.3 mmol/L [1,000 mg/dL]) should be treated pharmacologically because of associated risk of pancreatitis. Target <4.5 mmol/L [<400 mg/dL]

SPECIAL CASES

- **FAMILIAL HYPERCHOLESTEROLEMIA**—lifestyle modification and pharmacologic therapy with potent statin (atorvastatin, rosuvastatin) plus add-on therapy with bile-acid sequestrant or ezetimibe, or both. Consider PCSK9 inhibitor when available. Homozygotes may require LDL apheresis or possible liver transplantation (to provide functional LDL receptors). Consider genetic counseling for affected family members
- **FAMILIAL COMBINED HYPERLIPIDEMIA**—lifestyle modification (weight reduction and dietary changes) and pharmacologic therapy with statin plus add-on therapy with ezetimibe or fibrate
- **DYSBETALIPOPROTEINEMIA**—identify and treat comorbidities (diabetes, obesity, hypothyroidism). Pharmacologic therapy often unnecessary, but when needed, consider statin or fibrates. Consider genetic counseling (for apoE2 gene) for affected family members

TREATMENT ISSUES (CONT'D)

- **CHYLOMICRONEMIA SYNDROME**—dietary modification (total fat restriction initially until TG <11.3 mmol/L [1,000 mg/dL] then fat-limited diet), alcohol abstinence, optimize glycemic control, and discontinue offending medications. Pharmacologic therapy with fibrate plus add-on therapy with statin or orlistat

SPECIFIC ENTITIES

METABOLIC SYNDROME (syndrome X or insulin resistance syndrome)—National Cholesterol Education Program's Adult Treatment Panel (ATP) III report criteria ≥3 of the following five features:

- ↑ **TGL**— ≥ 1.7 mmol/L [≥150 mg/dL]
- ↓ **HDL**—♀ <1.30 mmol/L [<50 mg/dL], ♂ <1.04 mmol/L [<40 mg/dL]
- **INSULIN RESISTANCE**—fasting glucose ≥5.6 mmol/L [≥100 mg/dL] (modified; originally defined as fasting glucose ≥6.1 mmol/L [≥110 mg/dL])
- **WAIST CIRCUMFERENCE**—♂ >102 cm [>40 in.], ♀ >88 cm [>35 in.]. May consider ethnic-specific cut-offs where appropriate (Europid ♂ ≥94 cm [≥37 in.], ♀ ≥ 80 cm [≥31.5 in.]; South Asian/Chinese: ♂ ≥90 cm [≥35.5 in], ♀ ≥80 cm [31.5 in.]; Japanese: ♂ ≥85 cm [33.5 in.], ♀ ≥90 cm [35.5 in.])
- **HYPERTENSION**— ≥ 130/85 mmHg or on treatment

FAMILIAL DYSLIPIDEMIAS (FREDRICKSON CLASSIFICATION)

Type	Mechanism	Lipid profile	Tendon xanthoma	Palmar xanthoma	Eruptive xanthoma	Xanthelasma	Tuberous xanthoma	Cardiac risk
Type I. Hyperchylomicronemia (LPL deficiency)	LPL deficiency resulting in chylomicron accumulation	↑↑ TGL			✓	✓		-
Type IIa. Familial hypercholesterolemia	LDL receptor defect	↑ TC (LDL) +/− ↑ TG +/− ↑ apoB	✓			✓	✓	++
Type IIb. Familial combined hyperlipidemia	↑ hepatic production of VLDL	↑ apoB +/− ↑ TG +/− ↑ TC (LDL)				✓	(sometimes)	+
Type III. Dysbetalipoproteinemia	ApoE Δ (apoE2/E2); ↓ clearance of chylomicron and VLDL remnants	↑ TGL ↑ TC (VLDL, IDL)	(sometimes)	✓		✓	✓	+ (and PVD)
Type IV. Hypertriglyceridemia	↑ hepatic production of VLDL	↑ TC (VLDL) ↑ TGL ↓ HDL			✓	✓		+
Type V. Mixed hypertriglyceridemia	↑ production and ↓ clearance of VLDL and chylomicrons	↑↑ TGL ↑ TC (VLDL)			✓	✓		-

Smoking Issues

See SMOKING ISSUES (p. 480)

Approach to ECG

AHA/ACCF/HRS 2009 Recommendations
Circulation 2007 115:10
Circulation 2009 119:10

TEN STEPS TO ECG

1. **ID**—name and age, date, technique (12 lead, calibration, paper speed)
2. **RATE**—normal 60–100 beats/min. 300/150/100/75/60/50 rule
3. **RHYTHM**—regular/irregular, wide/narrow complex, sinus, atrial, atrioventricular, ventricular
4. **AXIS**—deviation, rotation
5. **PR INTERVAL**—normal 120–200 ms; first, second, third degree AV block
6. **QRS INTERVAL**—normal 80–110 ms, intraventricular conduction delay 110–120 ms, RBBB, LBBB, LAFB, LPFB
7. **QT INTERVAL**—QT <50% of RR interval; normal QTc 390–460 ms (women), 390–450 ms (men)
8. **HYPERTROPHY/ENLARGEMENT**—RAE, LAE, RVH, LVH
9. **ISCHEMIA**—ST elevation/depression, T wave inversion
10. **INFARCTION**—Q waves
11. **SPECIAL CONDITIONS**

CHEST LEADS PLACEMENT

V1—4th intercostal space, right sternal border
V2—4th intercostal space, left sternal border
V3—halfway between V2 and V4
V4—5th intercostal space, left mid-clavicular line
V5—5th intercostal space, left anterior axillary line
V6—5th intercostal space, left mid-axillary line

RATE AND RHYTHM

SINUS—P before QRS, QRS after P, P upright I + II, P down aVR. Normal (rate 60–100), tachycardia (rate >100), bradycardia (rate <60), arrhythmia (variable)
ATRIAL—rate 60–80 normally, variable P wave, short PR interval
JUNCTIONAL (mid and distal region of AV node)—rate 40–60, no P wave or inverted P wave
VENTRICULAR (His bundle, bundle branches, ventricle)—rate 20–40, no P wave

TACHYCARDIA

REGULAR NARROW COMPLEX TACHYCARDIA—sinus tachycardia, atrial flutter with fixed block (rate 300, 150, 100), supraventricular tachycardia (atrial tachycardia, AV nodal reentry, orthodromic AVRT (WPW), accelerated junctional tachycardia
IRREGULAR NARROW COMPLEX TACHYCARDIA—sinus tachycardia/arrhythmia, premature atrial contractions, multifocal atrial tachycardia, ectopic atrial tachyarrhythmia with variable block, atrial flutter with variable block, atrial fibrillation
REGULAR WIDE COMPLEX TACHYCARDIA—ventricular tachycardia, supraventricular tachycardia with aberrant conduction, pacemaker-mediated tachyarrhythmia, antidromic AVRT (WPW), metabolic abnormality (e.g., TCA overdose, hyperkalemia), artifact
IRREGULAR WIDE COMPLEX TACHYCARDIA—monomorphic ventricular tachycardia (during "warm-up phenomenon"), polymorphic ventricular tachycardia, atrial fibrillation with pre-excitation (WPW), irregular supraventricular tachycardia with aberrant conduction, coarse ventricular fibrillation, artifact
DISTINGUISHING FEATURES SUGGESTIVE OF VT RATHER THAN SVT WITH ABERRANT CONDUCTION—older age, history of coronary artery disease (>90% pre-test probability), history of structural heart disease (>90% pre-test probability), AV dissociation (dissociated P waves, fusion beats, capture beats), atypical bundle branch block morphology, concordance of precordial leads, QRS width >160 ms in LBBB or >140 ms in RBBB, extreme LAD (−90° to −180°). Hemodynamic stability (or instability) is not a useful distinguishing feature

BRADYCARDIA AND PROLONGED PR

SINUS—sinus bradycardia, sick sinus syndrome / sinus node dysfunction, sinus exit block, tachycardia-bradycardia syndrome (SSS + AF usually)
AV BLOCK—prolonged PR interval

- **FIRST DEGREE**—PR >200 ms constantly
- **SECOND DEGREE**

BRADYCARDIA AND PROLONGED PR (CONT'D)

- **MOBITZ TYPE I** (Wenckebach)—PR progressively longer and then dropped QRS
- **MOBITZ TYPE II**—PR constant and then sudden dropped QRS. When any but not all ventricular beats are dropped, second degree block exists

• **THIRD DEGREE**—complete blockage with independent atrial and escape rhythms (junctional or ventricular escape)

PROLONGED QRS—BUNDLE BRANCH BLOCK AND HEMIBLOCK

ANATOMY—SA node (RCA 59%, LAD 38%, both 3%) → AV node (RCA 90%, LCX 10%) → bundle of His (RCA) → right bundle (LAD), left anterior fascicle (LAD, RCA), and left posterior fascicle (RCA, LAD)

RBBB—QRS ≥120 ms, slurred S wave in I and V6 and rSR′ in V1–3 with R′ taller than r. May also see QR′ complex in V1 (suggestive of old or new infarct). QRS polarity positive in V1–2. Causes include LAD involvement/anterior infarction, may be benign in young people

LBBB—QRS ≥120 ms, broad notched or slurred R in I, aVL, V5, and V6, with no Q waves; broad monomorphic S in V1, may have small r wave. QRS polarity negative in V1–2. Causes include hypertension, CAD, dilated cardiomyopathy, rheumatic heart disease, infiltrative diseases, benign or idiopathic

LEFT ANTERIOR FASCICULAR BLOCK—QRS <120 ms, left axis deviation −45° to −90°, qR in aVL, R-peak time in aVL of 45 ms or more. May be benign, LAD involvement/anterior infarction. Shortcut to diagnosis—I up, II down, aVF down

LEFT POSTERIOR FASCICULAR BLOCK—right axis deviation 90–180°, QRS <120 ms, rS in I and aVL, and qR in III and aVF

PROLONGED QT

NORMAL—QTc = square root (QT in seconds/RR interval in seconds); QT <50% of RR interval; normal QTc 390–460 ms (women), 390–450 ms (men)

CAUSES—**genetic**, **metabolic** (hypokalemia, hypomagnesemia, hypocalcemia), **antiarrhythmics** (quinidine, procainamide, amiodarone, sotalol), **antibiotics** (macrolide, trimethoprim–sulfamethoxazole, fluoroquinolone), **psychotropics** (TCA, SSRI, haloperidol, risperidone), **analgesics** (methadone), **structural heart disease** (HF, LVH, acute ischemia), **others** (HIV, anorexia nervosa, stroke, brain injury)

PROLONGED QT (CONT'D)

PROGRESSION—may result in torsades de pointes, VT, and sudden death (amiodarone less likely)

TREATMENTS—remove offending agent(s), overdrive pacing, isoproterenol infusion, magnesium

HYPERTROPHY CRITERIA

RAE—tall peaked P in II and aVF (>2.5 mm high); large initial component of biphasic P in V1 (p pulmonale)

LAE—wide notched P in II (>2.5 mm long); biphasic P in V1 with broad negative phase; P wave duration >120 ms (p mitrale)

LVH—tall R in aVL (>11 mm); R in V5 or V6 (whichever is taller) plus S in V1 >35 mm; R in V5 or R in V6 > 27 mm; poor R wave progression in precordial leads; ST depression and T wave inversion in lateral leads (I, aVL, V5–6) suggestive of ventricular strain; R in aVL plus S in V3 >28 mm in male or >20 mm in female (Cornell criteria). Diagnosis difficult with LBBB, consider LVH if S in V1 + R in V5 >45 mm (Klein criteria)

RVH—right axis deviation (>110°); R > S wave in V1 and R >7 mm; persistent S waves V5–6; ST depression and T wave inversion V1–3

DIFFERENTIAL DIAGNOSIS FOR DOMINANT R WAVE IN V1—RV hypertrophy, right bundle branch block, posterior myocardial infarction, pre-excitation (Wolff–Parkinson–White), dextrocardia, Duchenne muscular dystrophy, hypertrophic cardiomyopathy, normal variant, incorrect lead placement, juvenile pattern

ISCHEMIA/INFARCT MORPHOLOGY

HYPERACUTE T WAVES—starts in seconds

ST ELEVATION—transmural injury, starts in minutes

ST DEPRESSION—subendocardial infarction. Consider posterior infarct if in V1/V2

T WAVE INVERSION—starts in hours, stays for weeks, and flips back in months

Q WAVES—starts in 8 h. If no reperfusion, stays forever. Considered significant if >1 block wide and height >1/3 of QRS

ACCELERATED IDIOVENTRICULAR RHYTHM—suggests reperfusion post-infarction (HR <100, intermittent)

VOLTAGE CRITERIA

NORMAL—QRS >5 mm high in limb leads, QRS >10 mm high in precordial leads

LOW—thick chest wall, COPD, pericarditis, pleural effusion, amyloidosis, myxedema, hemochromatosis

DIFFERENTIAL DIAGNOSIS OF ST ELEVATION

NORMAL MALE PATTERN—1–3 mm elevation, concave, most marked in V2

ST ELEVATION OF NORMAL VARIANT—seen in V4–5, short QT, high QRS voltage

BENIGN EARLY REPOLARIZATION—most marked in V4 with notching at J point, upright T waves. Reciprocal ST depression in aVR, not in aVL, when limb leads are involved

ACUTE MI—ST segment with a plateau of shoulder or upsloping, reciprocal behavior between aVL + III

PRINZMETAL'S ANGINA—same as MI but transient

ACUTE PERICARDITIS—diffuse ST elevation, ST depression in aVR. Elevation seldom >5 mm, PR segment depression (best seen in II)

ACUTE MYOCARDITIS—diffuse ST elevation, may simulate acute MI/pericarditis

AORTIC DISSECTION—obstruction of right coronary artery by dissection flap

LV ANEURYSM—persistent ST elevation after MI

DIFFERENTIAL DIAGNOSIS OF ST ELEVATION (CONT'D)

PULMONARY EMBOLISM—changes simulating MI seen often in both inferior and anteroseptal leads

STRESS (TAKOTSUBO) CARDIOMYOPATHY—transient apical and/or mid LV systolic dysfunction that mimics myocardial infarction, in the absence of obstructive CAD

LBBB—concave, ST segment deviation discordant from QRS. In the presence of LBBB, features suggestive of infarction include concordant ST segment changes (ST elevation ≥1 mm in leads with positive QRS complex and ST depression ≥1 mm in V1–3), disconcordant ST-segment changes (ST elevation ≥5 mm in leads with negative QRS complex) (Sgarbossa criteria)

LVH—concave, other features of LVH

HYPERKALEMIA—see below

HYPOTHERMIA—Osborne waves may be seen

NEJM 2003 349: 22

INFARCTION ZONES

Territory	Leads	Artery	Comment
Inferior	II, III, aVF[a]	RCA, LCX[b]	RV, SA, AV nodes
Lateral	I, aVL, V5, V6	LCX, RCA	
Posterior	V1i, V2i, V8, V9[c]	RCA	
Anterior	V1–V4[d]	LAD	May be massive LV
RV	R leads (V1), V4R	RCA	Preload

[a]Evidence of inferior MI should trigger one to automatically check V4R to assess for RV infarction, which occurs in up to 40% of patients with inferior MI. May see increased JVP and clear lung fields clinically. ST elevation in V4R is diagnostic and prognostic

[b]Inferior infarcts may be related to either RCA (ST elevation in III > II and ST depression in I, aVL, or both >1 mm) or LCX (ST elevation in I, aVL, V5–6 and ST depression in V1–3)

[c]i = inverted. ST depression in V1–V2 in a regular ECG should trigger one to automatically request for posterior leads to check for posterior MI. Posterior infarct may be associated with inferior and lateral infarct as these territories are all supplied by RCA

[d]V1–V2 = septal, V3–V4 = anterior

SPECIAL CONDITIONS

HYPERTHYROIDISM—tachycardia, non-specific ST-T changes, biphasic T in V2–V6

DIGITALIS EFFECT—slowing SA, AV. Gradual downward sloping/scooping of ST. ST depression in I, II, aVF, V2–V6

DIGITALIS TOXICITY—unifocal or multifocal PVCs, first degree heart block, ventricular bigeminy, paroxysmal atrial tachycardia (often with 2:1 AV conduction), bidirectional VT, atrial fibrillation with complete heart block (regular escape rhythm)

SPECIAL CONDITIONS (CONT'D)

HYPERKALEMIA—tall, peaked T wave (especially precordial leads. Definitions of "tall T wave" include a height >5 mm in limb lead or 10 mm in precordial lead or a T wave height >50% of the entire QRS excursion in same lead), widened QRS, wide and flat P wave

HYPOKALEMIA—flattened T wave/inversion, U wave

COPD—RAD, ↓ amplitude, multifocal atrial tachycardia

SPECIAL CONDITIONS (CONT'D)

HYPERCALCEMIA—short QT
HYPOCALCEMIA—prolonged QT
WOLFF–PARKINSON–WHITE SYNDROME—short PR (<120 ms), delta wave, prolonged QRS (>120 ms), symptomatic tachycardia. Pharmacological treatments include amiodarone and procainamide. **AV nodal blocking drugs** (**adenosine**, **β-blockers**, **verapamil**/**diltiazem**, **digoxin**) **are contraindicated in patients with WPW and AF as they may precipitate VF**. Consider catheter ablation if symptomatic arrhythmias, AF, or atrial flutter. If failed, consider surgical ablation
BRUGADA SYNDROME—type 1: high take-off and cove-shaped ST-segment elevation (≥2 mm) in V1–V2. Type 2: saddle-back ST-T pattern in V1–V2

3
NEPHROLOGY

Alan W. McMahon

Acute Renal Failure: Pre-renal

NEJM 2007 357:8

DIFFERENTIAL DIAGNOSIS

TRUE INTRAVASCULAR FLUID LOSS

- **HEMORRHAGE**
- **GI LOSS**—diarrhea, vomiting
- **RENAL LOSS**—diuretic, osmotic
- **SKIN LOSS**—increased insensible losses, sweating, burns

DECREASED EFFECTIVE CIRCULATING FLUID

- **HEART FAILURE**
- **HYPOALBUMINEMIA**—protein-losing enteropathy, nephrotic, cirrhosis, malnutrition
- **THIRD SPACING**
- **SEPSIS**

ALTERED RENAL HEMODYNAMICS

- **AFFERENT**—renal artery stenosis (RAS), fibromuscular dysplasia, ASA, NSAIDs, cyclosporin, tacrolimus, cocaine, hypercalcemia (vasospasm)
- **EFFERENT**—ACE inhibitors, ARB, renal vein thrombosis

PATHOPHYSIOLOGY

RISK FACTORS—patients with advanced age, hypertension, chronic kidney disease, renal artery stenosis, or on medications (NSAIDs, ACE inhibitors, ARBs) are particularly susceptible to ischemic insults due to impaired auto-regulation

Related topic
Renal Artery Stenosis (p. 65)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, Ca, urinalysis, urine lytes, urine Cr
- **MICROBIOLOGY**—blood C&S, urine C&S

SPECIAL

- **RENAL ARTERY STENOSIS WORKUP**—renal Doppler, captopril renogram, CT/MR renal angiogram (use with caution in renal failure)

DIAGNOSTIC ISSUES

COCKCROFT–GAULT FORMULA

- **CREATININE CLEARANCE (SI UNITS)**—CrCl = (140–age) × (weight in kg)/(Cr in μmol/L), multiply by 1.2 if male
- **CREATININE CLEARANCE (US UNITS)**—CrCl = (140–age) × (weight in lbs × 0.37)/(Cr in mg/dL × 88.4), multiply by 1.2 if male
- **NOTE**—creatinine is used to estimate GFR, but 5% of creatinine is secreted and thus overestimates GFR. At low GFR, proportion of creatinine secreted becomes higher, so overestimates even more

FEATURES SUGGESTING PRE-RENAL CAUSES

- **UREA:CR RATIO**—(urea in mmol/L × 10) > Cr in μmol/L [or in US units: (urea in mg/dL/20) > Cr in mg/dL]. Urea reabsorption increases during pre-renal failure, resulting in a disproportionally high serum urea level
- **10–20–30 RULE**—urine Na^+ <10 mmol/L or Cl^- <20 mmol/L and K^+ >30 mmol/L
- **FENA**—$(U_{Na}/P_{Na})/(U_{Cr}/P_{Cr}) \times 100\%$, <1%
- **URINALYSIS**—bland, high specific gravity

DISTINGUISHING FEATURES BETWEEN PRE-RENAL FAILURE AND ATN

	Pre-renal	ATN
Urea:Cr ratio (SI)	(Urea × 10) > Cr	(Urea × 20) < Cr
Urea:Cr ratio (US)	Urea > (Cr × 20)	Urea < (Cr × 10)
Increase in Cr	Variable	<44 μmol/L/day [<0.5 mg/dL/day]
Urinalysis	Normal	Heme granular casts
Urine Na	<20 mmol/L	>30 mmol/L
FE_{Na}	<1%	>2%
Urine osmo	>500 mOsm/kg	<350 mOsm/kg

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MANAGEMENT

TREAT UNDERLYING CAUSE—fluid resuscitation (**NS** 0.5–1 L IV bolus over 2–4 h), then 100–200 mL/h with frequent volume reassessments

RENAL REPLACEMENT—**dialysis** (peritoneal, hemodialysis). If needed, usually temporary

TREATMENT ISSUES

CRITERIA FOR DIALYSIS IN ACUTE RENAL FAILURE

★AEIOU★

- **ACIDOSIS**—persistent despite medical treatment
- **ELECTROLYTES**—persistent severe hyperkalemia despite medical treatment
- **INTOXICATION**—ASA, Li, methanol
- **OVERLOAD**—persistent fluid overload despite medical treatment
- **UREMIA**—pericarditis, encephalopathy

Acute Renal Failure: Renal

DIFFERENTIAL DIAGNOSIS

VASCULAR

- **EMBOLI**—atherothrombotic, cholesterol
- **MICROANGIOPATHIC HEMOLYTIC ANEMIA**—TTP, HUS, scleroderma, malignant hypertension
- **VASCULITIS**—PAN, Takayasu's
- **HYPERTENSION**—chronic

TUBULAR

- **ACUTE TUBULAR NECROSIS (ATN)**—ischemia, sepsis, contrast dye, aminoglycosides, amphotericin, acyclovir, myoglobin, hemoglobin, uric acid
- **INTRA-TUBULAR OBSTRUCTION**—uric acid, indinavir, calcium oxalate, acyclovir, methotrexate, light chains (myeloma)

INTERSTITIAL (ACUTE INTERSTITIAL NEPHRITIS, AIN)

- **IATROGENIC**—proton pump inhibitors, penicillins, cephalosporins, sulfonamides, rifampin, NSAIDs, diuretics
- **INFECTIONS**—pyelonephritis
- **INFILTRATE**—Sjogren's, sarcoidosis
- **IDIOPATHIC**

GLOMERULAR

- **NEPHROTIC**—MCD, MGN, FSGS, MPGN-I rarely if ever cause acute renal failure on their own
- **NEPHRITIC**—IgA, MPGN-II, mesangial proliferative GN, RPGN
  - **ANTI-GBM ANTIBODY**—Goodpasture's, anti-GBM antibody nephritis
  - **IMMUNE COMPLEX**—SLE, HBV, HCV, endocarditis, post-strep/infectious GN, IgA, cryoglobulinemia, shunt nephritis
  - **PAUCI-IMMUNE**—granulomatosis with polyangiitis (GPA), Churg–Strauss, microscopic polyarteritis (MPA)

CLINICAL FEATURES

HISTORY—duration (previous Cr), N&V, diarrhea, blood loss, obstructive urinary symptoms (frequency, urgency, hesitancy, slow stream, incontinence), hemoptysis, hematuria, edema, contrast dye, nephrotoxins, past medical history (recent infections, HBV, HCV, HF, diabetes, hypertension, malignancy, connective tissue disease), medications (ACE inhibitors, ARB, NSAIDs, ASA, cyclosporine, penicillins, cephalosporins, acyclovir, amphotericin, chemotherapy)

PHYSICAL—orthostatic vitals especially heart rate and blood pressure, respiratory and cardiac examination (JVP, heart failure), abdominal examination (masses, renal bruit), ankle edema, cholesterol emboli

Related Topic
Glomerulonephritis (p. 80)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, urinalysis, urine lytes, urine Cr
- **ETIOLOGY WORKUP**—ANA, anti-dsDNA, ENA, p-ANCA, c-ANCA, anti-GBM antibody, C3, C4, CK, uric acid, ASO-titer, HBV/HCV serology, RF, cryoglobulin, quantitative Ig, serum protein electrophoresis, urinary protein electrophoresis, urine eosinophils
- **MICROBIOLOGY**—blood C&S, urine C&S if suspect infection
- **IMAGING**—US renal

SPECIAL

- **IMAGING**—CXR, echocardiogram
- **SPECIAL**—renal biopsy

INVESTIGATION ISSUES

DISTINGUISHING FEATURES BETWEEN VARIOUS RENAL ETIOLOGIES

	Urinalysis	Other tests
Vascular	Bland	Peripheral smear (TTP)
	Urinary eosinophils (cholesterol emboli)	p-ANCA
		ANA (lupus), ENA
Tubular	Muddy brown casts (ATN)	CK (rhabdomyolysis)
		Uric acid (gout)
Interstitial	WBC casts, urinary eosinophils	Systemic eosinophilia
Glomerular	RBC casts	c-ANCA (GPA)
	Acanthocyte (dysmorphic RBC)	p-ANCA
	Oval fat body	Eosinophilia (Churg-Strauss)
	Fatty cast	Anti-GBM (Goodpasture's syndrome)
		ANA, anti-dsDNA (SLE)
		ASO titer (PSGN)
		Blood C&S, echo (infectious endocarditis)
		HBV/HCV serology, SPE, UPE (multiple myeloma)
		Cryoglobulins, rheumatoid factor (cryoglobulinemia)

MANAGEMENT

PREVENTION—**avoid contrast dye**, **nephrotoxins** if possible

TREAT UNDERLYING CAUSE—**nephrotic syndrome** (low-salt diet and furosemide for volume regulation if needed; statin if needed to correct hyperlipidemia)

RENAL REPLACEMENT—**dialysis** (peritoneal, hemodialysis)

SPECIFIC ENTITIES

PSEUDO-RENAL FAILURE—cimetidine and trimethoprim may reduce tubular secretion of creatinine causing a small but significant increase in serum creatinine in the absence of ↓ GFR

MULTIPLE MYELOMA AND RENAL FAILURE

- **PRE-RENAL**—N&V, renal vein thrombosis, calcium-induced vasospasm, nephrogenic diabetes insipidus (hypercalcemia)
- **RENAL**—secondary amyloidosis (**λ**), light chain deposition disease (**κ**), myeloma kidney (tubulointerstitial damage due to increased light chain absorption through proximal tubule), Bence Jones/cast nephropathy, plasma cell infiltration, cryoglobulinemia, pyelonephritis, sepsis
- **POST-RENAL**—renal stones (hypercalcemia), neurogenic bladder

NSAID-INDUCED RENAL FAILURE

- **PRE-RENAL**—inhibition of prostaglandin synthesis leading to afferent vasoconstriction, hypertensive nephropathy
- **RENAL**—acute interstitial nephritis, nephrotic syndrome (minimal change disease, membranous)

SPECIFIC ENTITIES (CONT'D)

ACUTE TUBULAR NECROSIS (ATN)

- **PATHOPHYSIOLOGY**—tubular damage → decreased reabsorption of Na → vasoconstriction → decreased GFR. Also may be related to tubular blockage from damaged epithelial cells. Risk factors include elderly (GFR ↓ by 1 mL/min/year after age 40), pre-existing renal dysfunction, decreased cardiac function, diabetes, dehydration, and multiple nephrotoxins
- **TREATMENTS**—after the insults are stopped, may start to recover in 3–5 days. Generally takes 7–21 days (some up to 8 weeks) for full recovery

CONTRAST NEPHROPATHY

- **PATHOPHYSIOLOGY**—contrast-induced vasospasm, hyperosmolar load and oxygen free radical generation → acute tubular injury → ↑ Cr or ↓ GFR by 25%. Usually develops immediately after exposure to contrast, peaks in 48–72 h. Risk factors and recovery time course same as ATN. Key differential diagnosis is renal atheroemboli after arterial catheterization (usually delayed onset of renal failure and may see other signs of arterial ischemia)
- **RISK FACTORS**—patient risk factors (pre-existent renal failure, multiple myeloma, diabetes mellitus, hypertension, volume contraction, HF, exposure to nephrotoxins such as NSAIDs or aminoglycosides, recent acute coronary syndrome), procedural risk factors (increased dye load, increased osmolar dye load)

SPECIFIC ENTITIES (CONT'D)

- **PREVENTION**—avoid contrast dye, nephrotoxins, and volume depletion if possible. If contrast absolutely required, use low (iohexol) or isoosmolal (iodixanol) non-ionic agents. Hydration options include (1) IV 1/2 NS at 1 mL/kg/h starting 12 h before until 12 h after contrast exposure; (2) IV NS *or NaHCO3* 154 mmol/L at 3 mL/kg/h starting 1 h before until 6 h after contrast exposure; (3) IV *N-acetylcysteine* 150 mg/kg in 500 mL 0.9% NS given 30 min before contrast exposure, followed by 50 mg/kg in 500 mL 0.9% NS IV given over 4 h after (alternatively, *N-acetylcysteine* 600 mg PO BID on day of and day after contrast exposure)

Acute Renal Failure: Post-renal

DIFFERENTIAL DIAGNOSIS

URETHRA—stricture, stenosis
PROSTATE—BPH, prostatitis, cancer
BLADDER—cancer, stones, clots, neurogenic
URETERS (bilateral involvement)

- **INTRALUMINAL**—cancer, stones, clots, papillary necrosis
- **EXTRALUMINAL**—cancer, retroperitoneal fibrosis, pregnancy

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, Cr/urea, urinalysis
- **IMAGING**—US abd/pelvis

INVESTIGATIONS (CONT'D)

SPECIAL

- **POST-RESIDUAL VOLUME**—>200 mL suggests obstruction
- **CT ABD/KUB/IVP**—if suspect stones or tumors
- **DIURESIS RENOGRAPHY OR UROGRAPHY**

DIAGNOSTIC ISSUES

RENAL US—hydronephrosis suggests post-renal causes. However, retroperitoneal fibrosis and acute post-renal obstruction may not show hydronephrosis

MANAGEMENT

TREAT UNDERLYING CAUSE—**Foley** catheter. For BPH (*tamsulosin* 0.4 mg PO daily or TURP)
RENAL REPLACEMENT—**dialysis** (peritoneal, hemodialysis)

Glomerulopathies

PATHOPHYSIOLOGY OF GLOMERULOPATHIES

AUTOIMMUNE PHENOMENON—antibodies binding to structural components of glomeruli (more glomerular basement membrane and podocytes involvement in nephrotic syndrome, more mesangium and endothelium involvement in nephritic syndrome), circulating antigen–antibody complexes, and/or cell-mediated immunity → further immune activation and damage to glomeruli

PATHOPHYSIOLOGY OF GLOMERULOPATHIES (CONT'D)

PATHOLOGY TERMS—**focal** = <50% of glomeruli, **diffuse** = > 50% of glomeruli, **segmental** = segment of glomerulus, **global** = entire glomerulus

CLINICAL FEATURES

CLINICAL MANIFESTATIONS OF GLOMERULAR DISEASES

Clinical manifestation	Examples
Asymptomatic proteinuria	FSGS, mesangial proliferative GN, diabetic nephropathy
Nephrotic syndrome	MCD, FSGS, MGN, MPGN, amyloidosis, light chain deposition disease, diabetic nephropathy
Asymptomatic hematuria	Thin basement membrane disease, IgA nephropathy, Alport's syndrome
Recurrent gross hematuria	Thin basement membrane disease, IgA nephropathy, Alport's syndrome

CLINICAL FEATURES (CONT'D)

Clinical manifestation	Examples
Acute nephritis	Post-infectious GN, IgA nephropathy, lupus nephritis, MPGN
Rapidly progressive glomerular nephritis (RPGN)	See text
Pulmonary-renal syndrome	Antiglomerular basement membrane antibody disease, immune complex vasculitis, pauci-immune (ANCA) vasculitis
Chronic renal failure	Sclerosed glomerular disease

DISTINGUISHING FEATURES BETWEEN NEPHROTIC AND NEPHRITIC SYNDROMES

	Nephrotic	Nephritic
Onset	Slower	Faster
Edema	++++	++
Blood pressure	N/↓	↑
Volume/JVP	N/↓	↑
Proteinuria	>3 g/day	May be <3 g/day
Hematuria	May occur	+++
Urine sediment	Hyaline casts, lipid droplets (oval fat body)	Dysmorphic RBC, WBC, RBC casts, granular casts
Albumin	↓↓↓	N/mild ↓
Creatinine	N/↑	Usually ↑
Serum Na	May be ↓↓	N/mild ↓

NOTE: nephrotic syndrome ≠ nephrotic range proteinuria (proteinuria >3 g/day without other symptoms and signs)

NEPHROTIC SYNDROME

DIFFERENTIAL DIAGNOSIS—minimal change disease, membranous GN, focal segmental glomerulosclerosis, MPGN (type 1), diabetes, amyloidosis, IgA nephropathy, HIV, drug-associated (NSAIDs, gold, pamidronate)

CLINICAL FEATURES—proteinuria (>3 g/day), edema, hypoalbuminemia, hyperlipidemia, lipiduria, hypercoagulability

INVESTIGATIONS—CBCD, lytes, urea, Cr, 24-h urine for protein and Cr, spot urine protein/Cr ratio, renal biopsy (simplification/effacement of visceral podocyte foot processes, classically non-inflammatory), lipid profile

POOR PROGNOSTIC FACTORS—male, age >50, ↑ creatinine, proteinuria >10 g/day, proteinuria >6 months, hypertension

TREATMENTS—Na restriction, blood pressure control, ACE inhibitor/ARB, treatment of dyslipidemia, steroid, cyclophosphamide, cyclosporine, anticoagulate if high risk

COMPLICATIONS—ARF/hypovolemia, malnutrition, hyperlipidemia, infections (especially encapsulated bacteria), arterial/venous thrombosis (30–40%), renal vein thrombosis, edema

NEPHRITIC SYNDROME

DIFFERENTIAL DIAGNOSIS—MPGN (type 2), rapidly progressive/crescentic GN (anti-GBM, immune, pauci-immune), IgA nephropathy

CLINICAL FEATURES—hematuria, proteinuria, hypertension, azotemia

INVESTIGATIONS—CBCD, lytes, urea, Cr, ANA, anti-dsDNA, ENA, p-ANCA, c-ANCA, anti-GBM, C3, C4 (complements low except for IgA nephropathy), CK, uric acid, ASO titer, HBV serology, HCV serology, cryoglobulin, quantitative Ig, serum protein electrophoresis, renal biopsy

TREATMENTS—steroid, cyclophosphamide, mycophenolate mofetil, rituximab

SPECIFIC ENTITIES

MINIMAL CHANGE DISEASE (MCD)

- **PATHOPHYSIOLOGY**—T-cell abnormality → ↑ glomerular permeability
- **CAUSES**—primary, secondary (NSAIDs, Li, interferon, NHL, Hodgkin's, leukemia, HIV, mononucleosis)
- **CLINICAL FEATURES**—pure nephrotic (minimal hematuria, no RBC casts, creatinine not elevated)

SPECIFIC ENTITIES (CONT'D)

- **PATHOLOGY**—light microscopy (normal), immunofluorescence (no immune complexes), electron microscopy (effacement of podocyte foot processes)
- **TREATMENTS**—steroid, cyclophosphamide, cyclosporine
- **PROGNOSIS**—90% steroid responsive, 10% steroid resistant, end-stage renal disease rare

MEMBRANOUS GN (MGN)

- **CAUSES**—primary, secondary (gold, penicillamine, captopril, solid tumors (breast, colon, and lung), Hodgkin's, SLE, rheumatoid arthritis, autoimmune thyroiditis, syphilis, HBV, HCV, chronic transplant rejection)
- **CLINICAL FEATURES**—pure nephrotic (minimal hematuria, no RBC casts)
- **PATHOLOGY**—light microscopy (basement membrane thickening, spikes), immunofluorescence (immune complexes IgG, and complements in subepithelial space), electron microscopy (same as immunofluorescence)
- **TREATMENTS**—steroid, cyclophosphamide, cyclosporine or tacrolimus
- **PROGNOSIS**—40% remission, 30% stable, 30% end-stage renal disease over 10–20 years

FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS) (more severe form of MCD)

- **CAUSES**—primary, secondary (Li, heroin, lymphomas, HIV. May also be associated with sickle cell disease, hypertension, and obesity)
- **CLINICAL FEATURES**—pure nephrotic (minimal hematuria, no RBC casts)
- **PATHOLOGY**—light microscopy (segmental areas of sclerosis), immunofluorescence (no immune complexes), electron microscopy (effacement of podocyte foot processes)
- **TREATMENTS**—steroid, cyclophosphamide, cyclosporine or tacrolimus
- **PROGNOSIS**—large percentage with end-stage renal disease over 15–20 years

MEMBRANOPROLIFERATIVE GN (MPGN)

- **PATHOPHYSIOLOGY**—type 1 = immune complex deposition disease. Type 2 = activation of complement system via C3 nephritic factor (IgG against C3 convertase), with decreased C3 and normal C4
- **CAUSES**—primary, secondary type 1 (HCV, HBV, endocarditis, abscess, infected shunts, CLL, lymphomas, SLE, cryoglobulinemia), secondary type 2 (partial lipodystrophy, sickle cell, complement deficiency)
- **CLINICAL FEATURES**—50% nephrotic (usually type 1), 20% asymptomatic proteinuria/hematuria, 30% acute nephritic (usually type 2)

SPECIFIC ENTITIES (CONT'D)

- **PATHOLOGY**—light microscopy (basement membrane thickening, mesangial cell hypercellularity), immunofluorescence (complements along capillary walls), electron microscopy (type 1 shows discrete deposits in mesangium, type 2 shows deposits as continuous ribbon in glomerular basement membrane)
- **TREATMENTS**—steroid, cyclophosphamide, cyclosporine
- **PROGNOSIS**—40–75% end-stage renal disease over 10–15 years

RAPIDLY PROGRESSIVE GN (RPGN)—ANTI-GLOMERULAR BASEMENT MEMBRANE ANTIBODY DISEASE

- **PATHOPHYSIOLOGY**—antibody against $\alpha 3$ chain of type IV collagen
- **CAUSES**—Goodpasture's syndrome, anti-GBM antibody nephritis
- **CLINICAL FEATURES**—nephritic (hematuria, proteinuria, ARF). Goodpasture syndrome also has lung involvement whereas anti-GBM antibody nephritis affects kidney alone
- **PATHOLOGY**—immunofluorescence (linear staining)
- **TREATMENTS**—plasmapheresis with IV pulse steroids followed by PO steroids with PO cyclophosphamide for 1 year

RAPIDLY PROGRESSIVE GN (RPGN)—IMMUNE COMPLEX

- **PATHOPHYSIOLOGY**—deposition of circulating immune complex in glomeruli, usually in subendothelial location
- **CAUSES**—SLE, HBV, HCV, endocarditis, post-strep GN, post-infectious GN, IgA nephropathy, cryoglobulinemia, shunt nephritis
- **CLINICAL FEATURES**—nephritic (hematuria, proteinuria, ARF)
- **PATHOLOGY**—immunofluorescence (granular staining)
- **TREATMENTS**—IV pulse steroids followed by PO steroids with IV monthly cyclophosphamide for 1 year, rituximab. If infection related, treat underlying infection

RAPIDLY PROGRESSIVE GN (RPGN)—PAUCI-IMMUNE COMPLEX

- **CAUSES**—granulomatosis with polyangiitis (c-ANCA), microscopic polyangiitis (p-ANCA), Churg–Strauss
- **CLINICAL FEATURES**—nephritic (hematuria, proteinuria, ARF). May have lung involvement
- **PATHOLOGY**—immunofluorescence (no staining)
- **TREATMENTS**—IV pulse steroids followed by PO steroids with PO cyclophosphamide for 1 year, rituximab

SPECIFIC ENTITIES (CONT'D)

IGA NEPHROPATHY

- **PATHOPHYSIOLOGY**—abnormal regulation of production or structure of IgA in response to environmental antigens → illness triggers production of IgA and/or IgA immune complex → deposit in mesangium
- **CAUSES**—primary, secondary (HSP, celiac disease, dermatitis herpetiformis, cirrhosis, HIV, malignancies, seronegative spondyloarthropathies)
- **CLINICAL FEATURES**—50% recurrent macroscopic hematuria with URTI, 30–40% persistent microhematuria and proteinuria, 10% rapidly progressive renal failure, <10% nephrotic syndrome
- **PATHOLOGY**—light microscopy (focal or diffuse mesangial hypercellularity and matrix expansion), immunofluorescence (extensive IgA deposition in mesangium and capillary walls), electron microscopy (mesangial deposits). Patients presenting with nephrotic syndrome may also have nephrotic histologic picture. Note most of the time IgA nephropathy is a clinical diagnosis. No biopsy unless ARF or severe symptoms
- **TREATMENTS**—ACE inhibitor may slow progression. Steroids, cytotoxic agents
- **PROGNOSIS**—20–40% end-stage renal disease over 20 years

Related Topics
Acute Renal Failure (p. 78)
Chronic Kidney Disease (p. 83)

Chronic Kidney Disease NEJM 2007 357:13

DIFFERENTIAL DIAGNOSIS

CAUSES OF ACUTE RENAL FAILURE—prerenal, renal, post-renal (see ACUTE RENAL FAILURE p. 78)

CHRONIC KIDNEY DISEASES

- **RENOVASCULAR DISEASE**—atherosclerosis, hypertensive nephropathy, glomerulosclerosis (with age)
- **DIABETES**—proteinuria
- **GLOMERULONEPHRITIS**
- **POLYCYSTIC KIDNEY DISEASE**
- **MULTIPLE MYELOMA**
- **NEPHROTOXINS**—NSAIDs

PATHOPHYSIOLOGY

DEFINITION OF CHRONIC KIDNEY DISEASE—>3 months of abnormal renal function, suggests irreversible component

CLASSIFICATION OF CHRONIC KIDNEY DISEASE

- **STAGE I** (GFR ≥90 mL/min/1.73 m^2, proteinuria)—observe, consider ACE inhibitor
- **STAGE II** (GFR 60–89 mL/min/1.73 m^2)—consider ACE inhibitor, nephrology referral
- **STAGE IIIa** (GFR 45–59 mL/min/1.73 m^2)—nephrology referral
- **STAGE IIIb** (GFR 30–44 mL/min/1.73 m^2)—nephrology referral
- **STAGE IV** (GFR 15–29 mL/min/1.73 m^2)—consider renal replacement therapy (dialysis or transplantation)

PATHOPHYSIOLOGY (CONT'D)

- **STAGE V** (GFR <15 mL/min/1.73 m^2)—dialysis, transplantation, or palliation

RISK FACTORS FOR CHRONIC KIDNEY DISEASE DEVELOPMENT AND PROGRESSION—old age, hypertension, proteinuria (not just a surrogate marker), high-protein diet, dyslipidemia

CLINICAL FEATURES

SIGNS AND SYMPTOMS OF CHRONIC KIDNEY DISEASE

- **VOLUME OVERLOAD**
- **ELECTROLYTE/ACID–BASE BALANCE**—hyperkalemia
- **METABOLIC ACIDOSIS**
- **NORMOCYTIC ANEMIA**
- **CALCIUM/PHOSPHATE BALANCE**—↓ 1,25$(OH)_2$ vitamin D3 synthesis in kidney, ↑ PO_4 due to decreased filtration → ↓ Ca → ↑ PTH → renal osteodystrophy (**osteitis fibrosa** with increased bone resorption from secondary hyperparathyroidism; **osteomalacia** with decreased bone resorption and unmineralized bone due to aluminum binder use (now uncommon); **adynamic bone disease** with decreased bone resorption due to oversuppression of PTH)
- **UREMIC SYMPTOMS**
- **CONSTITUTIONAL**—fatigue, generalized weakness
  - **NEUROLOGIC**—decreased memory and concentration, slow and slurred speech, myotonic jerks, seizures, altered smell and taste, peripheral neuropathy, sleep disturbances, restless leg syndrome

CLINICAL FEATURES (CONT'D)

- **GASTROINTESTINAL**—anorexia, nausea and vomiting, gastritis
- **HEMATOLOGIC**—anemia, platelet dysfunction, and bleeding
- **MUSCULOSKELETAL**—bone disorders, arthropathy, muscle cramps
- **DERMATOLOGIC**—pruritus, uremic frost, sallow
- **SEXUAL**—amenorrhea, sexual dysfunction, infertility

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, HbA1C, Ca, PO_4, Mg, PTH, albumin, fasting lipid profile, urinalysis, 24-h urinary albumin collection, 24-h urinary protein collection

SPECIAL

- **MYELOMA WORKUP**—serum protein electrophoresis, urinary protein electrophoresis

DIAGNOSTIC ISSUES

DISTINGUISHING FEATURES BETWEEN CHRONIC AND ACUTE RENAL FAILURE—previous creatinine (>3 months of elevated creatinine suggests CKD), anemia, small kidneys from renal US (except diabetes, amyloidosis, acromegaly, renal vein thrombosis, HIV nephropathy), renal osteodystrophy consistent with CKD. Renal biopsy is also helpful

MANAGEMENT

SLOW PROGRESSION

- **LIMIT PROTEIN INTAKE**—0.8–1 g/kg/day
- **ACE INHIBITION**—blood pressure and proteinuria control (*ramipril* 1.25–10 mg PO daily), renoprotective (see below)
- **LIPID CONTROL**
- **AVOID NEPHROTOXINS**
- **SMOKING CESSATION**
- **TREAT DIABETES MELLITUS, HYPERTENSION**

TREAT COMPLICATIONS

- **VOLUME OVERLOAD**—low-sodium diet, diuretics
- **HYPERKALEMIA** (K >5.5 mmol/L)—low-potassium diet, *hydrochlorothiazide* 12.5 mg PO daily, *kayexalate* 30 g PO daily-QID, decrease ACE inhibitor
- **METABOLIC ACIDOSIS**—consider $NaHCO_3$ if low pH or HCO_3
- **ANEMIA** (Hb <95 g/L [Hb <9.5 g/dL])—*epoetin alfa* 50–200 U/kg/week SC/IV div 2–3×/week, *darbepoetin alfa* 0.45 µg/kg SC every week, *ferrous fumarate* 600 mg PO qhs, goal to keep Hb 95–115 g/L [9.5–11.5 g/dL]

MANAGEMENT (CONT'D)

- **CALCIUM/PHOSPHATE BALANCE**—keep Ca normal, PO_4 <1.5 mmol/L [<4.6 mg/dL], PTH <2–3× normal, dietary phosphate restriction, phosphate binder *CaCO3* 500 mg PO TID, *calcitriol* 0.25–1 µg PO daily, parathyroidectomy

RENAL REPLACEMENT—**dialysis** (peritoneal, hemodialysis), **renal transplant**

TREATMENT ISSUES

CRITERIA FOR DIALYSIS IN CHRONIC KIDNEY DISEASE—GFR <10 mL/min/1.73 m^2, albumin <35 g/L [<3.5 g/dL], uremic symptoms, any acute indications

ACE INHIBITORS IN RENAL FAILURE—ACE inhibition leads to vasodilation of efferent arterioles → ↓ intraglomerular pressure → ↓ long-term remodeling/stress → slow progression of chronic kidney disease. Other positive effects of ACE inhibition include ↓ blood pressure, ↓ proteinuria, and ↓ mediators of glomerular tubule hypertrophy and fibrosis. Should start in all patients with chronic kidney disease ± hypertension ± proteinuria. If <30% rise in creatinine after starting ACE inhibitor, should continue as long-term benefit important. Expect GFR to return to pre-ACE inhibitor baseline after 3–4 months due to remodeling

SPECIFIC ENTITIES

DIABETIC NEPHROPATHY

- **NORMOALBUMINURIA** (<30 mg/day)—lasts 8–10 years, treatment with glycemic/blood pressure/lipid control, smoking cessation
- **MICROALBUMINURIA** (30–300 mg/day)—lasts 5–10 years, same treatment as above plus ACE inhibitor, protein restriction
- **OVERT NEPHROPATHY** (>300 mg/day)—CrCl declines by 2–20 mL/min/year, same treatment as above
- **PERCENTAGES**—25–40% of type 1 or 2 diabetics develop nephropathy: 99% of type 1 diabetics with chronic kidney disease are related to diabetes, while this is true only for 30% of type 2 diabetics

Related Topics
Acute Renal Failure (p. 78)
Diabetes Mellitus (p. 381)
Glomerulonephritis (p. 80)
Hypertension (p. 65)
Multiple Myeloma (p. 198)
Polycystic Kidney Disease (p. 86)

Proteinuria

DIFFERENTIAL DIAGNOSIS

FUNCTIONAL (<1 g/day)—infection, fever, exercise, orthostatic
TUBULAR (0.5–1 g/day)—interstitial nephritis, ATN
GLOMERULAR (1–3 g/day, usually >3 g/day)—nephrotic syndrome, nephritic syndrome, early diabetes
OVERFLOW (any amount but usually >1 g/day)—multiple myeloma

PATHOPHYSIOLOGY

DEFINITION OF PROTEINURIA—>150 mg/day of protein in urine. Physiologically, <150 mg of protein is secreted per day (Tamm-Horsfall mucoprotein mainly, with <30 mg albumin)
PROTEIN FILTRATION—based on size and charge. Large proteins such as albumin are usually retained by glomerular basement membrane (affected in glomerular proteinuria), while small proteins such as β_2 microglobulin filter through but are reabsorbed at proximal tubules (affected in tubular proteinuria)

CLINICAL FEATURES

HISTORY—ankle swelling, fever, strenuous exercise, urinary tract infections (dysuria, frequency), past medical history (myeloma, diabetes, glomerulonephropathies, lupus), medications (antibiotics, NSAIDs)
PHYSICAL—vitals particularly blood pressure, abdominal examination (cystic kidney), ankle edema, periorbital edema

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, HbA1C, fasting glucose, albumin
- **URINALYSIS**—inaccurate and dependent on urine volume, detects mainly negative charged proteins such as albumin and less so light chains
- **SULFOSALICYLIC ACID TEST**—detects all proteins
- **SPOT PROTEIN/CR RATIO** (SI Units)—to estimate daily protein excretion in mg
  ♂ = ratio × 0.14–0.16 mg/kg/day × weight in kg
  ♀ = ratio × 0.18–0.20 mg/kg/day × weight in kg
- **24-H URINARY PROTEIN**—most accurate but cumbersome method to quantify urinary protein

SPECIAL

- **MYELOMA WORKUP**—urinary protein electrophoresis, serum protein electrophoresis
- **KIDNEY BIOPSY**

MANAGEMENT

TREAT UNDERLYING CAUSE—observe if <1 g/day, urine benign and creatinine normal. Consider biopsy otherwise
SLOW PROGRESSION—ACE inhibitors

SPECIFIC ENTITIES

ORTHOSTATIC/POSTURAL PROTEINURIA—mainly in healthy young people. Split upright and recumbent urine collections could reveal protein loss mainly with upright position. Usually disappears with time and is of no clinical significance

Hematuria NEJM 2003 348:23

DIFFERENTIAL DIAGNOSIS

PIGMENTS—beets, myoglobinuria, hemoglobinuria, porphyrin, rifampin, food coloring
TRANSIENT—menstruation, urinary tract infections, fever, exercise (march hematuria), trauma, endometriosis, renal vein thrombosis
GLOMERULAR

- **NEPHRITIC SYNDROME**—MPGN II, RPGN, IgA nephropathy (see GLOMERULOPATHIES p. 80)

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **HEREDITARY DISORDERS**—Alport's syndrome, thin basement membrane disease, Loin pain hematuria syndrome

EXTRA-GLOMERULAR

- **TUMORS**—kidneys, ureters, bladder, urethra
- **STONES**
- **CYSTIC KIDNEY DISEASE**—polycystic kidney disease, medullary cystic kidney disease, medullary sponge kidney

PATHOPHYSIOLOGY

DEFINITION OF HEMATURIA—>1–2 RBC/high-power field

CLINICAL FEATURES

HISTORY—blood clots, other sources of bleeding (GI, hemoptysis, epistaxis), beets, fever, strenuous exercise, urinary tract infections (dysuria, frequency), last menstrual period, past medical history (tumors, renal stones, cystic kidney disease, lupus, Alport's syndrome), medications (ASA, NSAIDs, anticoagulants)
PHYSICAL—vitals (particularly blood pressure), check hearing, abdominal examination (cystic kidney)

INVESTIGATIONS

BASIC
- **LABS**—CBCD, lytes, urea, Cr, INR, PTT, urinalysis, urine C&S, urine cytology
- **IMAGING**—KUB, US abd, IVP, CT abd

SPECIAL
- **CYSTOSCOPY**—if suspect extra-glomerular bleed
- **KIDNEY BIOPSY**—if suspect glomerular pathology
- **URINE TESTS**—24-h urine calcium, oxalate, and urate

DIAGNOSTIC ISSUES

DIFFERENTIATING FEATURES FOR SOURCE OF BLEEDING
- **GLOMERULAR**—cola urine, proteinuria, dysmorphic RBC (acanthocytes), RBC casts, no clot

DIAGNOSTIC ISSUES (CONT'D)

- **EXTRA-GLOMERULAR**—bright red urine, no proteinuria, no dysmorphic RBC, clots, no RBC casts

MANAGEMENT

TREAT UNDERLYING CAUSE

SPECIFIC ENTITIES

ISOLATED PERSISTENT HEMATURIA—predisposition to stones, IgA nephropathy, Alport's syndrome, thin basement membrane disease, Loin pain-hematuria syndrome

ALPORT'S SYNDROME
- **PATHOPHYSIOLOGY**—X-linked defect in α5 chain of type IV collagen
- **CLINICAL FEATURES**—hematuria without proteinuria, may have hearing loss. End-stage renal disease by age 30–45 in males. Persistent microhematuria but rarely renal failure in female carriers

THIN BASEMENT DISEASE
- **PATHOPHYSIOLOGY**—autosomal dominant; defect of type IV collagen (usually α3 or α4 chain)
- **CLINICAL FEATURES**—hematuria without proteinuria. Normal GFR

Related topics
Glomerulonephritis (p. 80)
Polycystic Kidney Disease (p. 86)

Cystic Kidney Diseases

CAUSES

SIMPLE CYST
MALIGNANT CYST
AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE
MEDULLARY SPONGE KIDNEY
MEDULLARY CYSTIC KIDNEY DISEASE

INVESTIGATIONS

BASIC
- **LABS**—CBCD, lytes, Cr/urea, urinalysis
- **IMAGING**—US renal, IVP (medullary sponge kidney)

MANAGEMENT

TREAT COMPLICATIONS—infections, stones, dialysis if end-stage renal disease

SPECIFIC ENTITIES

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE
- **★The rule of 60's★**
- **PATHOPHYSIOLOGY**—autosomal dominant, affecting 1/400–1/1000 persons. 85% PKD1 (polycystin) mutation and 15% PKD2 mutation → multiple cysts formation in kidneys, liver, pancreas, ovaries, and spleen → cysts in renal cortex and medulla enlarge in size over years, cysts are prone to bleeding and infec-

SPECIFIC ENTITIES (CONT'D)

tions. Risk factors for progression include younger age at diagnosis, male, black, hypertension, and PKD1

- **CLINICAL FEATURES**—symptoms may include abdominal pain/fullness, microscopic hematuria (gross hematuria if cyst hemorrhages), hypertension, renal stone disease, recurrent UTI (cyst infections). Extrarenal involvements include cysts in other organs (liver **60**%), abdominal wall hernias (45%), colonic diverticuli, mitral valve prolapse (25%), and intracranial aneurysms (5–10%). Progression to end-stage renal disease <2% by age 40, 25% by age 50, 50% by age **60,** and 75% by age 70
- **DIAGNOSIS**—radiologic based on multiple cyst in kidneys (age <30, >2 cysts; age 30–60, 2 cysts in each kidney; age >**60**, ≥4 cysts in each kidney) in patients with a family history of PKD. No radiologic criteria exist for patients without a family history.
- **TREATMENTS**—blood pressure control, ACE inhibitors, dialysis if end-stage renal disease

NEJM 2008 359:14

SPECIFIC ENTITIES (CONT'D)

MEDULLARY CYSTIC KIDNEY DISEASE

- **PATHOPHYSIOLOGY**—genetic abnormality with diffuse tubulointerstitial cysts at corticomedullary border
- **CLINICAL FEATURES**—symptoms include hematuria and hypertension. Frequently progress to end-stage renal disease by age 20–50
- **TREATMENTS**—dialysis if endstage renal disease

MEDULLARY SPONGE KIDNEY

- **PATHOPHYSIOLOGY**—malformation of terminal collecting ducts bilaterally
- **CLINICAL FEATURES**—usually asymptomatic, but may see kidney stones, microscopic hematuria, or infections. Renal failure not likely. May see "brushlike" appearance of calyces in IVP
- **TREATMENTS**—treatment of stones and infections as needed

SIMPLE CYSTS

- **PATHOPHYSIOLOGY**—30% of men, 15% of women by age 70
- **CLINICAL FEATURES**—cortex affected. May be single or multiple. Usually round, well demarcated, smooth walls, no echoes within cyst, strong posterior wall echo. Asymptomatic and renal failure unlikely
- **DIAGNOSIS**—US renal every 6–12 months to help distinguish from cystic malignancy

Metabolic Acidosis

DIFFERENTIAL DIAGNOSIS

ANION GAP (NORMOCHLOREMIC)

- **★MUDPILE CATS★**
  - **METHANOL**
  - **UREMIA**
  - **DKA**
  - **PARALDEHYDE**
  - **INH AND IRON**
  - **LACTIC ACIDOSIS**
  - **ETHYLENE GLYCOL**
  - **CYANIDE**
  - **ARSENIC**
  - **TOLUENE**
  - **SALICYLATES**
- **★KULT★**
  - **KETONES**
  - **UREMIA**
  - **LACTIC ACIDOSIS**
  - **TOXINS**

DIFFERENTIAL DIAGNOSIS (CONT'D)

NON-ANION GAP (HYPERCHLOREMIC)

- **HCL GAIN**—drinking HCl
- **HCO_3 LOSS**—**renal** (proximal RTA, acetazolamide), **GI** (diarrhea, ostomy loss)
- **↓ HCO_3 PRODUCTION**—distal RTA, aldosterone deficiency/resistance
- **★HARD POPS★**
  - **HYPERALIMENTATION** (resulting from amino acid load in TPN)
  - **AMPHOTERICIN, ACETAZOLAMIDE**
  - **RENAL FAILURE, RTA** (type I, II, IV)
  - **DIARRHEA**
  - **PANCREATITIS, PANCREATIC FISTULA**
  - **OBSTRUCTIVE UROPATHY** (RTA IV)
  - **PEE** (ureteroenteric drain/ileal conduit)
  - **SALINE**

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, lactate, ketone, serum alcohol/methanol, serum osmolality, urinalysis, urine lytes
- **ABG**

SPECIAL

- **URINE OXALATE CRYSTALS**—if suspect ethylene glycol ingestion

Related Topics
Osmolar Gap (p. 116)
Overdose (p. 114)
Respiratory Acidosis (p. 22)
Respiratory Alkalosis (p. 22)

DIAGNOSTIC ISSUES

APPROACH TO ARTERIAL BLOOD GAS (ABG)

1. **Check accuracy of data**. $H^+ = 24 \times PCO_2/HCO_3$ (modified Henderson–Hasselbalch formula). Recollect ABG and lytes if discrepancy found
2. **Identify primary acid/base disturbance**
   - **Acidemia**—pH <7.35
   - **Alkalemia**—pH >7.45
   - **Acidosis/alkalosis**—disturbance in PCO_2 or HCO_3, irrespective of pH, that may result in acidemia/alkalemia, respectively
   - **Metabolic**—initiated by change in HCO_3
   - **Respiratory**—initiated by change in PCO_2
3. **Check compensation**

	Primary change HCO_3	Compensation pCO_2
MAc	↓ 10	↓ 10–13
MAlk	↑ 10	↑ 5–7
	pCO_2	**HCO_3**
RAlk	↓ 10	↓ 5 (chronic) 2 (acute)
RAc	↑ 10	↑ 3 (chronic) 1 (acute)

Normal pCO_2 = 40 mmHg, HCO_3 = 24 mmol/L

4. **Calculate anion gap** (↑ anion gap in MAc, ↓ anion gap may be due to hypoalbuminemia [10:2.5 ratio], paraproteinemia (e.g. myeloma), halide ingestion (e.g. lithium) or laboratory error)

   ANION GAP = Na – Cl – HCO_3; normal is between 8 and 12 mmol/L

4a. **If anion gap metabolic acidosis, calculate osmolar gap** to differentiate between causes **OSMOLAR GAP** = (**G**lucose + **U**rea + **N** $a^+ \times 2$) – observed osmolality ★**GUN2**★ (see p. 116 for more details)

DIAGNOSTIC ISSUES (CONT'D)

4b. **Calculate "delta ratio"** (also known as "delta-delta") to check for any superimposed metabolic disorder

$\Delta AG/\Delta HCO_3 = (AG - 10)/(24 - HCO_3)$

$\Delta AG/\Delta HCO_3$	**Interpretation**
<0.4	Combined ↑ AG MAc + non-AG MAc (i.e. ↓ HCO3 >> ↑ AG)
0.4–0.8	Possible ↑ AG MAc + non-AG MAc; typical for renal failure
1.0–2.0	Isolated ↑ AG MAc Lactic acidosis usually 1.6 DKA usually 1.0
>2.0	Combined ↑ AG MAc + MAlk, or Pre-existing compensated RAc (i.e. ↑ AG >> ↓ HCO3)

NOTE: be wary of over interpretation, use clinical judgment

5. **Any superimposed respiratory disorder?** After adjusting pCO_2 to account for HCO_3 changes (see compensation table above), is there evidence of hypoventilation (↑ pCO_2) or hyperventilation (↓ pCO_2)?

MANAGEMENT

ACUTE—ABC, O_2, IV, intubation, $NaHCO_3$ 1–2 amp IV bolus if pH <7.0

TREAT UNDERLYING CAUSE

SPECIFIC ENTITIES

LYTES AND URINE LYTES

- **ANION GAP METABOLIC ACIDOSIS**—serum chloride normal
- **URINE NET CHARGE** (UNC)—urine Na + K – Cl. In the presence of acidosis and normal renal function, UNC would be negative because NH_4^+ is excreted as the unmeasured cation (i.e. type II RTA, not type I RTA); remember to look for GI losses (neGUTive)

RENAL TUBULAR ACIDOSIS - TYPE I (distal)

- **PATHOPHYSIOLOGY**—inability to make NH_4^+. Causes include **H+/ATPase mutation** (associated with hypokalemia), **back leakage of hydrogen ions due to increased luminal membrane permeability** (Sjogren's syndrome, rheumatoid arthritis, amphotericin B, cirrhosis; associated with hyperkalemia) and **decreased distal tubular Na reabsorption resulting in reduced electrical gradient for proton secretion** (obstructive uropathy, sickle

SPECIFIC ENTITIES (CONT'D)

cell anemia; associated with hyperkalemia). Urine pH elevated because of ↓ H^+ in urine. Serum K ↓ in most cases

- **DIAGNOSIS**—positive UNC, urine pH inappropriately high despite metabolic acidosis
- **TREATMENTS**—treat underlying cause. HCO_3 and K supplement, or potassium citrate

RENAL TUBULAR ACIDOSIS – TYPE II (proximal)

- **PATHOPHYSIOLOGY**—inability to reabsorb HCO_3 at the proximal tubule. Causes include **Fanconi's syndrome** (multiple myeloma, carbonic anhydrase inhibitor, ifosfamide), **genetic disorders** (Wilson's disease, cystinosis), **vitamin D deficiency,** and **renal transplant**
- **DIAGNOSIS**—low serum K, negative urine net charge. Confirmation is done by HCO_3 challenge → check urine pH every 2 h → measure serum HCO_3 level when urine pH >7 (expect relatively "low" serum HCO_3 in type II RTA). Urinary pH initially ↑ due to HCO_3 loss, but then ↓ as serum HCO_3 becomes low

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—usually self-limiting in adults. HCO_3 supplement has limited utility due to HCO_3 wasting and may even lead to hypokalemia

RENAL TUBULAR ACIDOSIS – TYPE IV

- **PATHOPHYSIOLOGY**—causes include **hyporeninemic hypoaldosteronism** (renal failure, frequently diabetic nephropathy and sometimes acute glomerulonephritis, ACE inhibitors, NSAIDs), **primary aldosterone deficiency** (Addison's, congenital adrenal hyperplasia), and **aldosterone resistance** (amiloride, spironolactone, tubulointerstitial disease)
- **DIAGNOSIS**—high serum K
- **TREATMENTS**—K restriction in diet, diuretics. Fludrocortisone may be used with caution

DISTINGUISHING FEATURES FOR RENAL TUBULAR ACIDOSIS

	Type I	**Type II**	**Type IV**
Pathology	Distal	Distal Proximal	Ald deficiency
Serum K	↓/↑	↓	↑
Serum HCO3	Variable	10–20	>17
Urine pH	>**5.3**	Variable	<5.3
UNC	**Positive**	**Negative**	Variable

Metabolic Alkalosis

DIFFERENTIAL DIAGNOSIS

HCO_3 GAIN—**HCO_3 administration** (IV/PO), **citrate** (transfusion), **acetate** (TPN)

H^+ LOSS

- **GI LOSS**—vomiting, NG suction
- **PHYSIOLOGIC ALDOSTERONE-MEDIATED RENAL LOSS** (volume sensitive)
  - ↓ **FLUID INTAKE**
  - **RENAL LOSS**—diuretics, Bartter's, Gitelman's, hypomagnesemia
  - **GI LOSS**—vomiting, ileus, villous adenoma, stool Cl loss
  - **SKIN LOSS**—sweat, burn
  - **INTRACELLULAR ACIDOSIS**—hypokalemia
- **PATHOLOGICAL ALDOSTERONE-MEDIATED RENAL LOSS** (volume insensitive)
  - ↑ **RENIN**—renal artery stenosis, tumor
  - ↑ **ALDOSTERONE**—Conn's
  - ↑ **ALDOSTERONE-LIKE**—Cushing's

DIFFERENTIAL DIAGNOSIS (CONT'D)

★CLEVER PD★

- **CONTRACTION**
- **LICORICE**
- **ENDOCRINE**—Conn's, Cushing's, Bartter's
- **VOMITING**
- **EXCESS ALKALI**
- **REFEEDING ALKALOSIS**
- **POST-HYPERCAPNIA**
- **DIURETICS**

PATHOPHYSIOLOGY

FACTORS THAT POTENTIATE METABOLIC ALKALOSIS—↓ effective circulating fluid volume, hypokalemia, hyperaldosteronism, chloride deficiency

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, serum osmolality, urinalysis, urine lytes, magnesium, urine osmolality
- **ABG**

SPECIAL

- **SERUM ALDOSTERONE AND RENIN**

DIAGNOSTIC ISSUES

LYTES AND URINE LYTES

	U-Na	U-K	U-Cl	BP
Vomit HCl loss	↑	↑	↓	↓
Burn NaCl loss	↓	↑	↓	↓
Physiologic renal loss	↑	↑	↑	↓
Pathologic renal loss	↓	↑	↓	↑

URINE CHLORIDE

- **INCREASED** (>20 mmol/L, "Cl resistant")—diuretic use (decreased Cl reabsorption), Bartter's and Gitelman's syndrome (decreased Cl reabsorption), mineralocorticoid excess (Conn's), Cushing's syndrome, licorice, severe hypokalemia (impaired Cl transport), hypomagnesemia, alkali load, idiopathic
- **DECREASED** (<10 mmol/L, "Cl responsive")—decreased chloride intake, vomiting, NG drainage, post-diuresis, cystic fibrosis, villous adenoma, laxative abuse, persistent post-hypercapnia, RTA (decreased NH_4 excretion)

DIAGNOSTIC ISSUES (CONT'D)

MANAGEMENT

ACUTE—ABC, O_2, IV

TREAT UNDERLYING CAUSE—**volume sensitive** (fluids, replete K), **volume insensitive** (spironolactone, amiloride)

SPECIFIC ENTITIES

BARTTER'S SYNDROME—mutation of the Na–K–2Cl transporter in the thick ascending limb of Henle (similar to inhibition by loop diuretics). Characterized by hypercalciuria

GITELMAN'S SYNDROME—mutation of the Na–Cl transporter in the distal tubule (similar to inhibition by thiazide diuretics). Characterized by hypocalciuria

Hyponatremia NEJM 2000 342:21; NEJM 2007 356:20

DIFFERENTIAL DIAGNOSIS OF HYPOOSMOLAR HYPONATREMIA

HYPOVOLEMIC (VOLUME DEPLETION)

- **RENAL LOSS**—diuretics, hypoadrenalism, hypomagnesemia, Bartter's
- **GI LOSS**—vomiting, diarrhea, third spacing
- **SKIN LOSS**—sweat burns
- **BLOOD LOSS**

EUVOLEMIC

- **NON-SIADH MECHANISMS**
  - **ADRENAL INSUFFICIENCY**
  - **HYPOTHYROIDISM**
  - **PSYCHOGENIC POLYDIPSIA**
  - **LOW-SOLUTE DIET**—beer potomania, tea-and-toast syndrome
- **SIADH MECHANISMS**
  - **PHYSIOLOGIC RESPONSE**—stress, anxiety, pain, nausea
  - **CANCER**—SCLC, pancreatic, duodenum, thymoma, lymphoma
  - **LUNG DISEASE**—TB, abscess, empyema, pneumonia, viral pneumonitis
  - **CNS PROBLEMS**—skull fracture, subarachnoid hemorrhage, subdural hemorrhage, cerebral atrophy, encephalitis, meningitis, Guillain–Barre syndrome, lupus, acute intermittent porphyria
  - **DRUGS**—morphine, carbamazepine, TCA, chlorpropamide, vincristine, vinblastine, clofibrate, oxytocin, general anesthesia

HYPERVOLEMIC (edema)—cardiac failure, cirrhosis, GI-losing enteropathy, nephrotic syndrome, malnutrition

DIFFERENTIAL DIAGNOSIS OF HYPOOSMOLAR HYPONATREMIA (CONT'D)

PATHOPHYSIOLOGY

DEFINITION OF HYPONATREMIA—Na <135 mmol/L. The serum osmolality should be less than 275 mmol/L for hypoosmolar hyponatremia

INVESTIGATIONS

BASIC

- **LABS**—lytes, urea, Cr, glucose, TSH, cortisol, urine lytes, urine Cr, serum and urine osmolality (e.g. to rule out pseudohyponatremia)

DIAGNOSTIC ISSUES

VOLUME STATUS—the patient's volume status (hypovolemia, euvolemic, hypervolemic) helps to narrow the differential diagnosis and dictates the appropriate workup

SIADH CRITERIA—diagnosis of SIADH requires the following: cause available, clinically euvolemic, hyponatremic, increased urine osmolality (>100 mmol/L and usually >300 mmol/L), specific gravity (>1.003), increased urine Na (>40 mmol/L), and low uric acid. Also need to rule out hypothyroidism, adrenal insufficiency, diuretic use, and psychogenic polydipsia. See **NEJM 2007 356:20** for more details

CALCULATING CORRECTION RATE

- **CHANGE IN SERUM Na** = $(Na_{infusate} - Na_{serum})$/(total body water + 1) where total body water ≈ 0.5 × body weight (kg) in women and 0.6 × body weight (kg) in men
- **VOLUME OF INFUSATE NEEDED** (in liters) = intended change in serum Na over a defined period of time (usually 8 mmol/L over 24 h)/change in serum Na
- In patients with chronic hyponatremia, the **daily limit of increase in serum Na** should be ≤**8 mmol/L** to minimize the risk of central pontine myelinolysis (CPM). The initial rate of correction can still be 1–2 mmol/L per hour for several hours in patients with severe symptoms. In patients with acute hyponatremia, the daily limit can be more flexible
- **INFUSATE SODIUM CONTENT**—D5W (5% dextrose in water) 0 mmol/L, ½ NS (0.45% NaCl in water) 77 mmol/L, Ringer's lactate 130 mmol/L, NS (0.9% NaCl in water) 154 mmol/L, 3% hypertonic saline 513 mmol/L, 5% hypertonic saline 855 mmol/L

MANAGEMENT

HYPOVOLEMIC—**NS** infusion. 3 oxo cubes/L water daily × 3 days. Hypertonic saline or furosemide if severe (be extremely cautious)

EUVOLEMIC—**free water restriction** <1 L/days. Demeclocycline. NS or hypertonic saline (3%), plus furosemide if severe. Treat underlying cause

HYPERVOLEMIC—**Na and free water restriction** <1 L/day, bed rest. Treat underlying cause

TREATMENT ISSUES

VAPTANS ("**AQUARETICS**")—oral V2 receptor antagonists → block ADH action → water diuresis. For correction of euvolemic and hypervolemic hyponatremia, but requires close monitoring

TREATMENT ISSUES (CONT'D)

INDICATIONS FOR HYPERTONIC SALINE—severe symptoms such as seizures

FUROSEMIDE-INDUCED DIURESIS—equivalent to ½ isotonic saline solution. Thus, furosemide can be used to treat hyponatremia, particularly with the concurrent use of normal saline or hypertonic saline. Careful monitoring to avoid Na overcorrection.

SPECIFIC ENTITIES

PSEUDOHYPONATREMIA—severe paraproteinemia or hypertriglyceridemia

HYPEROSMOLAR HYPONATREMIA—hyperglycemia (correct Na by adding 3 mmol/L for every 10 mmol/L increase in glucose), hypertonic 3 mmol/L mannitol

ISOOSMOLAR HYPONATREMIA—glycine or sorbitol flushing solutions during transurethral resection

ACUTE HYPONATREMIA

- **PATHOPHYSIOLOGY**—very different from chronic hyponatremia. Usually develops postop due to ADH release from stress, pain, nausea, meds (morphine, chlorpromazine, carbamazepine), brain natriuretic peptide
- **DIAGNOSIS**—low Na
- **TREATMENTS**—compared to chronic hyponatremia, it is acceptable to correct Na rapidly to ~140 mmol/L with little risk of CPM

CENTRAL PONTINE MYELINOLYSIS

- **PATHOPHYSIOLOGY**—within first day of hyponatremia, brain swells as water shifts into cells to equilibrate osmotic gradient → brain cells extrude Na, K, and osmolytes to balance the gradient and to minimize cerebral edema → over next 2–3 days, brain volume returns to normal → rapid Na correction can lead to "shrinking" of brain cells or osmotic demyelination, particularly if Na increased by >12 mmol/L per day
- **CLINICAL FEATURES**—typically delayed 2–6 days (may be weeks) after correction and often irreversible. Symptoms include dysarthria, dysphagia, paraparesis, lethargy, coma, and seizures
- **RISK FACTORS**—alcoholics, ♀ on thiazide diuretics, patients with K^+, and burn victims
- **DIAGNOSIS**—CT head, MRI head
- **TREATMENTS**—dismal prognosis with no effective therapy. Careful avoidance of Na overcorrection is key

Hypernatremia NEJM 2000 342:20

DIFFERENTIAL DIAGNOSIS

HYPOVOLEMIC—decreased thirst, decreased water access

EUVOLEMIC (diabetes insipidus)

- **NEUROGENIC**—trauma, tumors, **infections** (TB, meningitis, encephalitis), **infiltrative** (sarcoidosis), vascular, idiopathic
- **NEPHROGENIC**—**renal disorders** (polycystic kidneys, infiltration, infection, ischemia), **hypercalcemia**, **medications** (lithium, demeclocycline, amphotericin B), **idiopathic**

HYPERVOLEMIC—drink seawater, excessive IV fluid, primary hyperaldosteronism

PATHOPHYSIOLOGY

DEFINITION OF HYPERNATREMIA—Na >145 mmol/L

CLINICAL FEATURES

SYMPTOMS—may include intense thirst, muscle weakness, confusion, and coma. Brain shrinkage could potentially cause vascular rupture, leading to cerebral bleeding, subarachnoid hemorrhage, permanent neurologic deficit, and death

INVESTIGATIONS

BASIC

- **LABS**—lytes, urea, Cr, glucose, Ca, serum osmolality, urinalysis, urine lytes, urine Cr, urine osmolality

SPECIAL

- **DDAVP TEST**—to distinguish between nephrogenic and neurogenic diabetes insipidus (DI)

DIAGNOSTIC ISSUES

CALCULATING CORRECTION RATE

- **WATER DEFICIT** (in liters)
  $= (Na_{current}/Na_{goal} - 1) \times$ total body water
- **CHANGE IN SERUM Na**
  $= (Na_{infusate} - Na_{serum})/(\text{total body water} + 1)$
  where total body water $\approx 0.5 \times$ body weight in women and $0.6 \times$ body weight in men
- **VOLUME OF INFUSATE NEEDED** (in liters) = intended change in serum Na over a defined period of time (usually 10 mmol/L over 24 h) divided by change in serum Na + 1.5 L to compensate for obligatory daily water losses
- **INFUSATE SODIUM CONTENT**—D5W (5% dextrose in water) 0 mmol/L, ½NS (0.45% NaCl in water) 77 mmol/L, Ringer's lactate 130 mmol/L, NS (0.9% NaCl in water) 154 mmol/L. Avoid using NS for correction of hypernatremia unless hemodynamic instability/fluid resuscitation

OSMOLALITY—urine osmolality is usually lower than serum osmolality in diabetes insipidus, whereas urine osmolality is usually higher than serum osmolality in hypovolemic hypernatremia

MANAGEMENT

HYPOVOLEMIC—**hypotonic fluid** infusion. Treat underlying cause

EUVOLEMIC—**ADH** if central diabetes insipidus. Free water hydration. Treat underlying cause (see POLYURIA p. 396)

Hypokalemia

DIFFERENTIAL DIAGNOSIS

↓ **INTAKE**—rare

SHIFT INTO CELL—metabolic alkalosis, hyperinsulin states, ↑ β-adrenergic states, hypothermia

↑ **OUTPUT**

- **GI LOSS**—diarrhea, vomiting, tube drainage
- **RENAL LOSS**—diuretics, hypomagnesemia, type I or II RTA, hyperaldosteronism, Conn's, renal artery stenosis

PATHOPHYSIOLOGY

DEFINITION OF HYPOKALEMIA—K <3.5 mmol/L

PHYSIOLOGY—daily intake of potassium is usually 40–120 mEq/day (banana contains 1 mEq of K every 2.5 cm [1 in.]), which is mostly excreted by the kidneys. In hypokalemia, renal excretion may decrease to 5–25 mEq/day

POTASSIUM DEFICIT—every 1 mmol/L decrease in serum K represents a loss of approximately

PATHOPHYSIOLOGY (CONT'D)

150–300 mmol of total body K. Males, younger age, and higher muscle mass may require replacement at the higher end of this range

HYPERALDOSTERONISM DUE TO HYPOVOLEMIA—usually does not lead to hypokalemia as it is counterbalanced by a decreased distal renal flow (which on its own would lead to decreased K excretion)

CLINICAL FEATURES

SYMPTOMS—usually not present unless K <2.5 mmol/L

- **MUSCULAR**—weakness or paralysis (periodic hypokalemia paralysis). May include extremities, respiratory and gastrointestinal muscles. Cramps, paresthesias, tetany, muscle tenderness, atrophy, and rhabdomyolysis may develop
- **CARDIAC**—arrhythmia includes sinus bradycardia, paroxysmal atrial or junctional tachycardia, AV block, VT, VF, ST depression, small T waves and U waves
- **RENAL**—impaired urinary concentrating ability (nocturia, polydipsia, polyuria), increased renal bicarbonate reabsorption, increased renal ammonia production due to intracellular acidosis, and hypokalemic nephropathy

INVESTIGATIONS

BASIC

- **LABS**—lytes, magnesium, urea, Cr, glucose, CK, serum osmo, urinalysis, urine lytes, urine osmo

SPECIAL

- **ECG**
- **HYPERALDOSTERONISM WORKUP**—serum aldosterone and plasma renin activity

MANAGEMENT

ACUTE (K <3.0 mmol/L)—***KCl*** 10 mEq in 100 mL D5W IV bolus × 3. For continuous infusion, maximum KCl concentration is 40 mEq/L

K SUPPLEMENT—***KCl*** 20–120 mEq PO divided over once daily to QID. Oral supplementation is preferred over intravenous in general. Need to replete Mg if low to facilitate correction of K (*MgSO4* 5 g IV over 4 h)

TREAT UNDERLYING CAUSE

Hyperkalemia

DIFFERENTIAL DIAGNOSIS

PSEUDOHYPERKALEMIA—hemolysed blood sample, leukocytosis, thrombocytosis

↑ **INTAKE**—rare

SHIFT OUT OF CELL—metabolic acidosis, diabetes (insulin deficit), β-blockade

↑ **RELEASE**—rhabdomyolysis, tumor lysis, strenuous exercise, intravascular hemolysis

↓ **OUTPUT**

- ↓ **DISTAL TUBULAR FLOW**—renal failure, ↓ effective circulating fluid volume
- **HYPOALDOSTERONISM**—↓ renin, adrenal insufficiency, type IV RTA, ACE inhibitors, ARBs, spironolactone, NSAIDs

PATHOPHYSIOLOGY

DEFINITION OF HYPERKALEMIA—K >5.0 mmol/L

CLINICAL FEATURES

SYMPTOMS

- **MUSCULAR**—weakness and even paralysis of extremities, but rarely respiratory muscle involvement
- **CARDIAC**—tall, peaked T wave (especially precordial leads), widen QRS, wide and flat P wave, VF

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, CK, serum osmolality, urinalysis, urine lytes, urine osmolarity
- **ECG**—consider if K >6.0 mmol/L. May see peaked T waves

SPECIAL

- **ABG/VBG**—quick way to get serum K level
- **HYPOALDOSTERONISM WORKUP**—serum aldosterone and plasma renin activity

MANAGEMENT

ACUTE (K >6.0 mmol/L with ECG changes)

- **STABILIZE MEMBRANE**—*calcium chloride* 10% 10 mL IV push, *calcium gluconate* 10% 10 mL IV push, do NOT give if hyperkalemia related to digoxin (can precipitate VF)
- **SHIFTING K INTO CELLS** (temporizing measure)
  - **INSULIN**—D50 50 mL IV push followed by *Humulin R* 10 U in 50 mL of D50% IV bolus. Consider dextrose drip or second amp of D50W as hypoglycemia occurs up to 70% of cases when only 1 amp of D50 given
  - **ALKALOSIS**—*NaHCO3* 45 mEq IV over 5 min, repeat in 30 min PRN for acidosis

MANAGEMENT (CONT'D)

- **β-AGONIST**—*salbutamol* 10–20 mg via NEB, monitor heart rate

REMOVAL OF K—*kayexalate* 30 g PO daily-QID (avoid if HF/Na retention), each dose followed by lactulose 30 mL PO. ***Ca resonium*** 30–40 g in 50 mL 20% sorbitol. **Diuretics** (*furosemide* 40 mg IV, doses up to 200 mg may be needed in ARF). **Dialysis**

TREAT UNDERLYING CAUSE—**discontinue drugs** (K supplements, ACE inhibitors, ARBs, spironolactone, NSAIDs, trimethoprim)

Hypomagnesemia

DIFFERENTIAL DIAGNOSIS

↓**INTAKE**—malnutrition, malabsorption, maldigestion

SHIFT INTO BONE—hungry bone syndrome

↑ **OUTPUT**

- **GI LOSS**—diarrhea, small bowel bypass surgery, acute pancreatitis
- **RENAL LOSS**—thiazide, loop diuretics, alcohol, hypercalcemia, tubular dysfunction (alcohol, aminoglycosides, amphotericin B, cisplatin, cyclosporine, acute tubular necrosis in diuretic phase, primary renal magnesium wasting)

PATHOPHYSIOLOGY

DEFINITION OF HYPOMAGNESEMIA—Mg <0.7 mmol/L [<1.4 mEq/L]

CLINICAL FEATURES

SYMPTOMS

- **LYTES/CA/PO4**—↓ K, ↓ Ca, PTH resistance, vitamin D deficiency

CLINICAL FEATURES (CONT'D)

- **HEART**—ventricular arrhythmias, widening of the QRS, peaking or diminution (severe) of T waves, prolongation of PR interval, and torsade de pointes

INVESTIGATIONS

BASIC

- **LABS**—lytes, urea, Cr, Ca, Mg, PO_4, serum osmolality, urinalysis, urine Mg, urine Cr

DIAGNOSTIC ISSUES

FeMg $= (U_{Mg}/U_{Cr})/(0.7 \times P_{Mg}/P_{Cr})$, <3 suggests extrarenal loss

MANAGEMENT

MG SUPPLEMENT—$MgSO_4$ 5 g IV over 5 h, *Mg gluconate* 500 mg PO TID

TREAT UNDERLYING CAUSE—amiloride may be used to prevent amphotericin B induced hypomagnesemia and hypokalemia

Hypophosphatemia

DIFFERENTIAL DIAGNOSIS

↓ **INTAKE**—alcoholism, inadequate intake, antacids

SHIFT INTO CELL—acute respiratory alkalosis (DKA, hyperventilation), hyperinsulin (especially refeeding syndrome), hungry bone syndrome

↑ **OUTPUT**

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **PRIMARY HYPERPARATHYROIDISM**
- **SECONDARY HYPERPARATHYROIDISM** (vitamin D deficiency/resistance)—hereditary hypophosphatemic rickets, oncogenic osteomalacia, Fanconi syndrome, osmotic diuresis, acetazolamide, acute volume expansion, steatorrhea, chronic diarrhea

PATHOPHYSIOLOGY

DEFINITION OF HYPOPHOSPHATEMIA—PO_4 < 0.8 mmol/L [<2.5 mg/dL]

CLINICAL FEATURES

SYMPTOMS

- **CNS** (intracellular ATP falls)—metabolic encephalopathy
- **MUSCULAR** (intracellular ATP falls)—↓ myocardial contractility, HF, respiratory failure, proximal myopathy, dysphagia, ileus, rhabdomyolysis
- **HEMATOLOGIC** (RBC 2,3 DPG falls)—hemolysis, ↓ WBC activity, ↓ clot retraction, thrombocytopenia

Related topics
Hypocalcemia (p. 401)
Vitamin D Deficiency (p. 401)

INVESTIGATIONS

BASIC

- **LABS**—Ca, Mg, PO_4, PTH, CK, 24-h urinary PO_4 collection (<100 mg), urine PO_4, urine Cr

DIAGNOSTIC ISSUES

$FePO_4 = (U_{PO4}/U_{Cr})/(P_{PO4}/P_{Cr})$, <5 suggests not due to ↑ output

MANAGEMENT

PO_4 SUPPLEMENT—**potassium phosphate** (22 mmol K^+, 15 mmol PO_4) in 250 mL NS over 4 h, or **sodium phosphate** (20 mmol Na^+, 15 mmol PO_4) in 250 mL NS over 4 h, or **sodium phosphate** 1 g PO TID (replaces ~100 mmol/day)
TREAT UNDERLYING CAUSE—**vitamin D deficiency** (*vitamin D* 800 U PO daily)

Ureteral Calculi NEJM 2004 350:7

CAUSES

CALCIUM (80%)—calcium oxalate or calcium phosphate, radiodense
URIC ACID (10–15%)—20% of patients also have gout, radiolucent
STRUVITE (10–15%)—urea-splitting bacteria (*Proteus*, *Klebsiella*), infected stone. Staghorn calculi if filled entire renal pelvis, radiodense
CYSTINE (1%)—autosomal recessive disorders of renal tubular absorption of dibasic amino acids, radiodense

PATHOPHYSIOLOGY

STONE FORMATION

- **PROMOTERS**—low urine volumes, urine cystine, pH (distal RTA), uric acid, Ca/oxalate/PO_4, anatomic defects (medullary sponge kidney)
- **INHIBITORS**—high urine volumes, urine citrate, Mg, Tamm-Horsfall proteins, nephrocalcin, uropontin, orthophosphates
- **COMPLICATIONS**—obstruction, renal failure, infection, urosepsis, ureteral stricture

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, Ca, PO_4, PTH, uric acid, urinalysis (artifact most times)
- **IMAGING**—unenhanced CT abd/pelvis (sens 96%, spc 100%), KUB (consider EWSL if see stone on film), US abd, IVP

INVESTIGATIONS (CONT'D)

SPECIAL

- **URINE TEST**—24-h urinary Ca/PO_4, oxalate, urate, Mg, citrate, and Na
- **CYSTOSCOPY**

DIAGNOSTIC ISSUES

RADIODENSE STONES—**★COLAS★** Calcium, Cystine, Ornithine, Lysine, Arginine, Struvite
RADIOLUCENT STONES—uric acid, matrix (organic substances associated with urea-producing bacteria), indinavir (radiolucent on X-ray and CT)

MANAGEMENT

ACUTE—**pain control** (*ketorolac* 30–60 mg IV/IM, then 15 mg IV/IM q6h or 10 mg PO q6h, *diclofenac* 50 mg PO BID–TID, or *morphine* 5 mg SC q4h). **N&V** (*dimenhydrinate* 25–50 mg PO/IV/SC q4h PRN, *metoclopramide* 10 mg PO/IV q4h PRN). **Urology consult** (if stone does not pass spontaneously or >5 mm, consider shock wave lithotripsy, ureteroscopy, percutaneous nephrolithotomy. If obstructed, infected upper urinary tract, impending renal deterioration, intractable pain/N&V, anuria or high-grade obstruction of solitary kidney, nephrostomy or insert stent). **Infection** (*ciprofloxacin* 500 mg PO q12h, or *ampicillin* and *gentamicin*; urosepsis from obstructing nephrolithiasis requires emergent decompression)

MANAGEMENT (CONT'D)

PREVENTION—↑ **daily fluid intake** (>2 L of water/day, or water plus 125 mL lemon juice/day). **Hypercalciuria** (dietary Na and protein restriction, do not restrict calcium intake, *hydrochlorothiazide* 25 mg PO daily-BID). **Hyperoxaluria** (diet oxalate restriction with ↓ spinach, chocolate, cocoa, beets, nuts, *Ca citrate* 1 g PO TID with meals). **Hypocitraturia** (*K citrate* 25 mEq PO BID or *Ca citrate* 1 g PO TID; avoid Na citrate). **Hyperuricosuria** (dietary uric acid restrictions, *allopurinol* 100 mg PO daily, alkalinization of urine with K citrate or $NaHCO_3$). **Hypomagnesuria** (*Mg gluconate* 500 mg PO TID)

Hypertension

See HYPERTENSION (p. 65)

Approach to Dialysis

HEMODIALYSIS

PRINCIPLES OF CLEARANCE—**fluid removal** (ultrafiltration ± osmotic gradient), **solute removal** (small toxins, middle molecules, electrolytes; dialysis by osmotic gradient). Urea is a surrogate marker and is not toxic itself

FACTORS AFFECTING EFFICIENCY—countercurrent exchange, blood pump speed, dialysate speed (500 mL/min), size of membrane, time (4–6 h 3× week)

VASCULAR ACCESS—temporary (double lumen internal jugular/femoral. Avoid subclavian placement if possible to minimize risk of subclavian stenosis), intermediate (PermCath internal jugular), permanent (AV graft, AV fistula)

ORDERS

- **GOAL WEIGHT DETERMINATION**—symptoms, clinical fluid status, blood pressure
- **FILTER**—low efficiency for new patients, high-flux, high-efficiency filters for most other patients
- **BLOOD PUMP SPEED**—usually 400–450 mL/min for CRF. May start at 200–250 mL/min for new patients
- **DIALYSATE FLOW**—500 mL/min
- **DURATION**—usually 4 h. May start at 2.5 h for new patients
- **FLUID REMOVAL**—net weight gain + fluid given during dialysis. Try to attain dry weight
- **Na+**—ramp 150–140 mmol/L or 150–135 mmol/L to keep intravascular osmolality high at beginning of run to maintain blood pressure. Otherwise, may simply set Na at 137 mmol/L or 140 mmol/L throughout the run. If hyponatremia, set Na at 132–135 mmol/L
- **K+**—as a general rule, [dialysate K] = 7 mmol/L – [serum K]. Careful with 1 K^+ bath

HEMODIALYSIS (CONT'D)

- **HCO_3**—25–40 mmol/L (usually 35 mmol/L)
- **CA^{2+}**—1.25–1.75 mmol/L [5–7 mg/dL] (usually 1.55 mmol/L [6 mg/dL])
- **TEMPERATURE**—35.5 °C [95.9 °F]
- **HEPARIN**—500 U bolus then 500 U/h if first time. Otherwise, 1000 U bolus then 500 U/h. If high risk (active bleed, HITT, anticoagulated), consider no heparin. Citrate is an alternative if HITT

ADEQUACY—goal KT/V 1.4/session (for 3×/week)

COMPLICATIONS OF INTERMITTENT HEMODIALYSIS

- **DIALYSIS DISEQUILIBRIUM SYNDROME**—high osmolar state in new patients just starting dialysis. With rapid removal of osmolality by dialysis intravascularly, can lead to shifting of fluid intracellularly and cerebral edema. Patients become confused and ↓ level of consciousness. See dialysis orders above for preventative measures
- ↓ **BLOOD PRESSURE DURING RUN**—too rapid removal of fluid, also see SHOCK p. 108 for other causes. Treatments include Trendelenburg position, stopping ultrafiltration, fluid bolus NS 100 mL, and consider ramping Na next time
- **MUSCLE CRAMPS**—due to rapid fluid removal. Give fluid bolus NS 100 mL, and consider ramping Na next time
- **ITCHING**—unknown cause. *Diphenhydramine* 50 mg × 1 dose or *hydroxyzine* 10–25 mg × 1 dose

CONTINUOUS RENAL REPLACEMENT THERAPY

TYPES—continuous arterial–venous hemofiltration (CAVHD) obsolete, continuous venous–venous hemofiltration (CVVHD), CVVHD + diffusion component

CONTINUOUS RENAL REPLACEMENT THERAPY (CONT'D)

INDICATIONS TO STOP CONTINUOUS RENAL REPLACEMENT—urine output increased, hemodynamically stable (consider switching to intermittent hemodialysis)

ADVANTAGES OF CONTINUOUS RENAL REPLACEMENT COMPARED TO INTERMITTENT HEMODIALYSIS—use in hemodynamically unstable patients (less likely sudden blood pressure drop), better in keeping metabolites low and stable, better in removing middle and larger molecular (especially in septic patients), better nutrition for patient can be provided

DISADVANTAGES OF CONTINUOUS RENAL REPLACEMENT—requires anticoagulation (heparin, citrate, NS flush q30 min), removes more solute, and requires more filter replacement

PERITONEAL DIALYSIS (PD)

ADVANTAGES OF PERITONEAL DIALYSIS COMPARED TO INTERMITTENT HEMODIALYSIS—better middle molecular clearance, better control of fluid and blood pressure, preserves residual renal function better, cheaper, increased patient autonomy

METHODS OF CLEARANCE—**continuous ambulatory peritoneal dialysis** (4×2 L exchanges/day for 30–40 min during the day, with one indwelling exchange overnight), **continuous cycler PERITONEAL DIALYSIS** (reverse timing of CAPD)

PERITONEAL DIALYSIS (PD) (CONT'D)

FACTORS AFFECTING EFFICIENCY—volume of exchanges, time of exchange, efficiency of peritoneal membrane (high average transporter vs. low average transporter)

DIALYSATE—**Dianeal** (standard with Na 132 mmol/L, Cl 95 mmol/L, Mg 0.25 mmol/L [5 mEq/L], osmolality 395 mmol/kg, pH 5.2, **dextrose** 0.5%, 1.5%, 2.5%, or 4.25%), **Extraneal** (icodextrin 7.5%), **Nutrineal** (1.1% amino acid solution. Good nutrition). Concentration of glucose affect fluid removal

ADEQUACY—goal KT/V 1.7/week and creatinine clearance 60 L/week

COMPLICATIONS OF PERITONEAL DIALYSIS

- **PERITONITIS**—once every 2 years. Triad of abdominal pain, cloudy dialysate, and >100 WBC/mm^3 (>50% PMN). Treat with intraperitoneal ceftazidime (or aminoglycoside) and vancomycin empirically until cultures available (add anti-fungal therapy if gram stain shows yeast)
- **MECHANICAL**—blockage (causes include constipation, omental wrap, tube in wrong position), leak, pleural effusion
- **METABOLIC**—hypokalemia, hyperglycemia (glucose in dialysate)
- **MEMBRANE**—lasts 6–8 years as glucose toxic to peritoneal membrane

4
CRITICAL CARE

Wendy Sligl

Intensive Care Issues

ICU ADMISSION CRITERIA

NEED FOR FREQUENT OR CONTINUOUS MONITORING—post-high-risk surgery, high risk for clinical deterioration

HIGH INTENSITY OF NURSING CARE

LIFE SUPPORT THERAPY—mechanical ventilation, vasoactive drugs, continuous renal replacement, artificial liver support

PREVENTATIVE STRATEGIES

VENTILATOR-ASSOCIATED PNEUMONIA—remove endotracheal tube as soon as possible, orotracheal intubation unless contraindicated, strict hand hygiene, oral and dental hygiene (chlorhexidine rinse), semi-recumbent positioning (head of bed at 30°), rotational bed therapy, subglottic suctioning, drainage of condensate from ventilator circuits, minimize gastric acid suppression therapy (proton pump inhibitors) when possible

GASTROINTESTINAL STRESS ULCERATION—risk factors include mechanical ventilation and/or coagulopathy. Prophylaxis with H_2 blockers (e.g. *ranitidine* 50 mg IV q8h or 150 mg PO/NG q12h) preferred unless high risk as use of proton pump inhibitors is associated with increased risk of ventilator-associated pneumonia

VENOUS THROMBOEMBOLISM—particularly in patients with trauma and prolonged bed rest. Prophylaxis includes heparin SC, LMWH, fondaparinux, or pneumatic compression stockings

SEDATION, ANALGESIA, PARALYSIS IN THE ICU

SEDATION/AMNESIA—*propofol* 0.5 mg/kg/h initial infusion, titrate to 0.5–3.0 mg/kg/h by continuous IV infusion, typical infusion range 0–300 mg/h. Appropriate for short-term sedation, monitor for acidosis and increased CK with prolonged use, rapid onset, short duration; *midazolam* 0.03 mg/kg loading dose, then 0.02–0.1 mg/kg/h IV infusion, typical infusion range 0–10 mg/h, rapid onset, short duration; *lorazepam* 0.5–10 mg IV q2–4 h PRN, load with 0.5–2 mg q15min, avoid continuous infusion as propylene glycol solvent may accumulate. Use for intermediate to prolonged sedation, longer duration than midazolam, most potent amnestic

SEDATION, ANALGESIA, PARALYSIS IN THE ICU (CONT'D)

ANALGESIA—*fentanyl* 50–100 μg q5min IV load to effect, then 1–4 μg/kg/h by continuous IV infusion, typical infusion range 50–300 μg/h, 100× more potent than morphine. Used in patients with hemodynamic instability, rapid onset, short duration (but highly lipophilic; may accumulate with prolonged infusion); *morphine* 0.05 mg/kg IV load, then 4–15 mg/h. May cause hypotension due to histamine release; *hydromorphone* 0.5 mg IV initially, then 1–2 mg q1h or 0.5–2 mg/h infusion, 5× more potent than morphine

NEUROMUSCULAR BLOCKAGE—*rocuronium* 0.5 mg/kg IV PRN, onset 1 min, duration 30 min; *pancuronium* 0.06–0.15 mg/kg IV PRN, onset 2–3 min, duration 60–120 min, may run continuous infusion 0.01–0.05 mg/kg/h, vagolytic effect may cause tachycardia; *cisatracurium* 0.15–0.2 mg/kg IV PRN, onset 2–3 min, duration 30 min, may run continuous infusion 3 μg/kg/min, undergoes Hoffman degradation; *succinylcholine* 0.5–1.5 mg/kg IV, onset 1 min, duration ~10 min, metabolized by pseudocholinesterase, many contraindications

DIFFERENTIAL DIAGNOSIS FOR WEAKNESS IN THE ICU

ENCEPHALOPATHY—hypoxic/ischemic, septic, hepatic, uremic, hypoglycemic, iatrogenic (drugs)

MYELOPATHY—hypoxic/ischemic, traumatic

NEUROPATHY—critical illness polyneuropathy, Guillain–Barré syndrome, motor neuron disease, compression, hypophosphatemia

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DIFFERENTIAL DIAGNOSIS FOR WEAKNESS IN THE ICU (CONT'D)

NEUROMUSCULAR JUNCTION—blocking agents, Eaton–Lambert, myasthenia gravis, hypomagnesemia, hypocalcemia, organophosphates, botulism

MYOPATHY—critical illness myopathy, acute necrotizing myopathy, hypokalemia, hypophosphatemia, hypocalcemia, hypomagnesemia, steroid, muscular dystrophy, polymyositis

PROCEDURES

RADIAL ARTERIAL LINE INSERTION (NEJM 2006 354:E13)

- **LANDMARK**—palpate radial artery immediately proximal to scaphoid. Insert 20-gauge (48 mm length) catheter at 30°

FEMORAL ARTERIAL LINE INSERTION

- **LANDMARK**—femoral artery is midway between ASIS and pubic symphysis. Puncture and insert catheter over the wire, *never dilate an artery!*

FEMORAL CENTRAL VENOUS CATHETER (NEJM 2008 358:E30)

- **LANDMARK**—femoral artery is midway between ASIS and pubic symphysis. Femoral vein is medial to artery. Insert introducer needle through skin at 45° toward umbilicus, about 1 cm below the inguinal ligament, then use Seldinger technique to place catheter
- **COMPLICATIONS**—arterial puncture (9–15%), hematoma (4%), infection (6–20%)

SUBCLAVIAN CENTRAL VENOUS CATHETER (NEJM 2007 357:E26)

- **LANDMARK**—subclavian vein is directly underneath clavicle. Insert introducer needle through skin at 20° 2 cm lateral and 2 cm caudal to the middle third of clavicle aiming toward sternal angle. When needle hits clavicle, apply downward pressure (so needle is parallel to clavicle) and slide it under inferior surface to puncture subclavian vein
- **KEY POINTS**—place patient in Trendelenburg position and occlude hubs at all times to avoid air embolism
- **COMPLICATIONS**—arterial puncture (6.3–9.4%), hematoma (<2.2%), pneumothorax (<0.2%), infection (0.12%)
- **REMOVAL**—place patient in Trendelenburg position and ask him/her to perform a Valsalva maneuver when removing the catheter to prevent air embolism

PROCEDURES (CONT'D)

INTERNAL JUGULAR CENTRAL VENOUS CATHETER (NEJM 2007 356:E21)

- **LANDMARK**—locate carotid pulse. Internal jugular is immediately lateral to carotid. Consider ultrasound guided internal jugular central venous catheter insertion to identify aberrant anatomy. Insert introducer needle through skin at 20° toward ipsilateral nipple, slightly superior to the apex of the triangle
- **KEY POINTS**—place patient in Trendelenburg position, avoid significant contralateral rotation as it may increase incidence of artery/vein overlap and decrease venous return, occlude hubs at all times to prevent air embolism
- **COMPLICATIONS**—arterial puncture (6.3–9.4%), hematoma (<2.2%), pneumothorax (<0.2%), infections (0.45%)
- **REMOVAL**—place patient in Trendelenburg position and ask him/her to perform a Valsalva maneuver when removing the catheter to prevent air embolism

NEJM 2003 348:12

CENTRAL VENOUS SATURATION

ARTERIAL OXYGEN CONTENT (CaO_2)

- $C_aO_2 = O_2$ carried by hemoglobin + O_2 dissolved in blood
- $C_aO_2 = 1.36 \times Hb \times S_aO_2 + 0.003 \times P_aO_2$ where S_aO_2 = arterial Hb saturation

VENOUS OXYGEN CONTENT (CvO_2)

- $C_vO_2 = O_2$ carried by hemoglobin + O_2 dissolved in blood
- $C_vO_2 = 1.36 \times Hb \times S_vO_2 + 0.003 \times P_vO_2$ where S_vO_2 = mixed venous Hb saturation ($S_{cv}O_2$ if using central venous saturation)

OXYGEN FLUX (DO_2)

- DO_2 = amount of oxygen delivered to tissues/min
- $DO_2 = CO \times C_aO_2$, where $C_aO_2 \sim 1.36 \times Hb \times S_aO_2$ since $0.003 \times P_aO_2$ is negligible

OXYGEN CONSUMPTION (VO_2)

- VO_2 = the arteriovenous oxygen content difference multiplied by cardiac output
- $VO_2 = CO \times (C_aO_2 - C_vO_2) \approx$ constant (the body normally extracts ~25% of the delivered oxygen except in fever, sepsis, hyperthyroidism, i.e. $VO_2/DO_2 = 0.25$)

INTERPRETATION

- As $CO \times (C_aO_2 - C_vO_2) \approx$ constant, $\downarrow C_vO_2$ suggests $\downarrow$ CO or $\downarrow O_2$ consumption from end-stage shock
- S_vO_2 is about 75% saturated. A mixed venous saturation of <50% is alarming, <25% is usually unsustainable

PROGNOSTIC ISSUES

ACUTE PHYSIOLOGIC AND CHRONIC HEALTH EVALUATION (APACHE) II SCORE—predicts hospital mortality, web-based programs are available. The latest version is APACHE IV

- **CLINICAL**—age, GCS, organ failure (biopsy-proven cirrhosis, NYHA class IV, severe COPD, chronic hemodialysis, immunocompromise), procedure (non-surgical, elective, emergency operation)
- **VITALS**—HR, RR, MAP, temp
- **ABG**—pH, A-a gradient or PaO_2
- **CBC**—Hct, WBC
- **CHEMISTRY**—Na, K, Cr

VENTILATION—95% of patients with acute respiratory failure can be weaned within 7 days of intubation. 5% are unable to be weaned from the ventilator and require tracheostomy and long-term ventilatory support

CARDIOPULMONARY RESUSCITATION

CONDITIONS ASSOCIATED WITH NEGLIGIBLE CHANCE OF SURVIVING CPR—**decompensated diseases** (cancer, sepsis, pre-arrest hypotension or hypoxia, anemia, chronic renal failure), **poor baseline function** (dependent on ADLs), **scene of CPR** (>10 min of CPR without the return of at least a single vital sign, unwitnessed arrest)

PROGNOSIS—respiratory arrest better than cardiac arrest. VT/VF/bradycardia better than asystole/PEA (patients with VF/VT witnessed arrest and response within 5 min of resuscitation have the highest probability of survival to discharge). Outcomes most favorable if resuscitated promptly; however, many have neurologic impairment, particularly if out-of-hospital arrest. Survival to discharge 1–5% for out-of-hospital CPR and 15% for in-hospital CPR

BRAIN DEATH

EXAMINATION OF THE UNRESPONSIVE PATIENT

- **VITALS**—including GCS
- **5 N**—neurological, noggin, neck, nose, needle
- **EYES**—fundoscopy, pupillary reflex, corneal reflex, oculocephalic reflex, oculovestibular reflex
- **OTHERS**—gag reflex, cough reflex, tone, limb reflexes, Babinski

GLASGOW COMA SCALE

- **EYES OPENING**—1 = none, 2 = to pain, 3 = to voice, 4 = voluntary
- **LANGUAGE**—1 = none, 2 = sounds, 3 = words, 4 = disorganized sentences, 5 = organized sentences/oriented

BRAIN DEATH (CONT'D)

- **MOTOR**—1 = none, 2 = extension to pain (decerebrate), 3 = flexion to pain (decorticate), 4 = withdraws, 5 = localizes to pain; 6 = obeys commands
- **CONSIDER INTUBATION**—if GCS <8, unable to protect airway

OCULOCEPHALIC REFLEX

- **DOLL'S EYES RESPONSE**—avoid this test in patients with suspected cervical spine injury. Move the patient's head from side to side. Conjugate eye movement in the opposite direction to head movement is expected in the comatose patient, while it may be absent/asymmetric if the patient has brain stem injury or if psychogenic

OCULOVESTIBULAR REFLEX

- **CALORIC TESTING**—instillation of ice-cold water into the ear canal on one side (ensure tympanic membrane intact prior to performing). Conjugate eye movement to the irrigated side is expected in the comatose patient (without nystagmus), while it may be absent or asymmetric if the patient has brain stem injury. In a conscious patient, nystagmus will be seen with the slow phase toward irrigated side and the fast phase toward the opposite side. Warm water instillation produces the opposite effect (★**COWS**★ In conscious patient instilled with **C**old water, nystagmus fast phase moves toward **O**pposite side; with **W**arm water, nystagmus fast phase moves toward **S**ame side)

ANOXIC BRAIN INJURY SPECTRUM

1. Good recovery (mild disability)
2. Moderate disability (independent with ADLs)
3. Severe disability (dependent for ADLs)
4. Persistent vegetative state (unawareness but awake at times)
5. Persistent coma (unawareness at all times but potentially reversible)
6. Brain death (unawareness at all times and irreversible)

DEFINITION OF BRAIN DEATH

- **HISTORY**—documentation of cause and irreversibility, absence of drug intoxication or poisoning, absence of hypothermia, absence of metabolic causes for encephalopathy
- **PHYSICAL**—core temperature ≥34 °C [≥93.2 °F], absence of motor response to painful stimulus, absence of brain stem reflexes (corneal, pupillary, gag, cough, doll's eyes, calorics), apnea testing
- **IMAGING**—perfusion scan (most sensitive test), cerebral angiogram, EEG, transcranial doppler ultrasound, somatosensory evoked potentials (SSEPs)

BRAIN DEATH (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES: IS THIS PATIENT DEAD, VEGETATIVE, OR SEVERELY NEUROLOGICALLY IMPAIRED (ASSESSING OUTCOME FOR COMATOSE SURVIVORS OF CARDIAC ARREST)?

	LR+	LR–
Clinical signs that predict death or poor neurological outcome		
Absent corneal reflexes at 24 h	12.9	0.60
Absent pupillary response at 24 h	10.2	0.8
Absent withdrawal response to pain at 24 h	4.7	0.2
No motor response at 24 h	4.9	0.6
No motor response at 72 h	9.2	0.7

APPROACH—"simple physical examination maneuvers strongly predict death or poor outcome in comatose survivors of cardiac arrest. The most useful signs occur at 24 h after cardiac arrest and earlier prognosis should not be made by clinical examination alone. These data provide prognostic information, rather than treatment recommendations, which must be made on an individual basis incorporating many other variables"

JAMA 2004 291:7

BRAIN DEATH (CONT'D)

- **CRITERIA**—need history, physical features and apnea testing to confirm brain death clinically. If apnea testing cannot be performed or indeterminate, ancillary testing required (cerebral blood flow most reliable 'stand alone' test)
- **BRAIN DEATH MIMICS**—locked-in syndrome (focal injury to pons), hypothermia (light reflex lost 28–32 °C [82.4–89.6 °F], other brain stem reflexes lost <28 °C [82.4 °F]), drug intoxication, Guillain–Barré syndrome

Related Topics
Dialysis Issues (p. 96)
Critical Illness Neuromuscular Disorders (p. 378)
Palliative Care (p. 439)
Resuscitation Status (p. 440)

APNEA TESTING

1. Obtain ABG just prior to test
2. Pulse oximetry on, ventilator off, 100% oxygen 6 L/min into trachea or place patient on bagger
3. Observe for respiratory movements. Obtain ABG after 8 min. Reconnect ventilator immediately and draw ABG if SBP <90 mmHg, marked decrease in SaO_2, or arrhythmia
4. Apnea present if respiratory movements are absent, $PaCO_2$ ≥60 mmHg or increased ≥20 mmHg above baseline

Hypoxemia

DIFFERENTIAL DIAGNOSIS

R TO L SHUNT (unresponsive to supplemental O_2, V/Q <1)—ARDS, HF, pneumonia, alveolar hemorrhage, atelectasis, pulmonary arteriovenous malformation, intracardiac shunt (ASD, VSD, PFO)

V/Q MISMATCH (V/Q >1)—pneumonia, ARDS, asthma, COPD, fibrosis, pulmonary embolism, tumor-filled alveoli, atelectasis, HF

DIFFUSION DEFECTS—interstitial lung disease, PJP, atypical pneumonia

HYPOVENTILATION (A-a normal)

- **CNS**—sedating drugs, tumor, stroke, sleep apnea

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **NEUROMUSCULAR**—botulism, Guillain–Barré, ALS, myxedema
- **UPPER AIRWAY OBSTRUCTION**—epiglottitis, laryngospasm
- **LOWER AIRWAY OBSTRUCTION**—COPD, asthma
- **DEAD SPACE VENTILATION**—COPD

LOW O_2 PARTIAL PRESSURE (A-a normal)—high altitude

PATHOPHYSIOLOGY

DEFINITION OF HYPOXEMIA—P_aO_2 < 60 mmHg. Note that hypoxia refers specifically to decreased oxygen supply to tissues and organs

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, troponin/CK, lactate
- **IMAGING**—CXR, CT chest
- **ABG**
- **ECG**

DIAGNOSTIC ISSUES

OXIMETRY

- **NORMAL**—>90% is normal. Dyspnea may occur ~85%. Pulmonary hypertension may develop from chronic alveolar hypoxia if saturations <80%
- **ACCURACY**—between 70 and 100% saturation error is ±2%. Saturation values <70% may not be valid. Most reliable when applied to well-perfused, warm, and motionless extremities. Nail polish, darkly pigmented skin, carboxyhemoglobin, methemoglobin may all affect readings. Co-oximetry required for accurate results (run ABG). Continuous oximetry is better than spot measurements
- **CORRELATION**—S_pO_2 50% = P_aO_2 27 mmHg, 75% = 40 mmHg, 90% = 60 mmHg, 92% = 80 mmHg, 95% = 90 mmHg. ABG is the gold standard for diagnosing hypoxemia

OVERALL APPROACH TO DETERMINING THE CAUSE OF HYPOXEMIA

1. Confirm ABG shows low P_aO_2
2. Exclude diffusion defects and low partial pressure of O_2
3. Check $PaCO_2$. If normal or low, then hypoventilation is excluded. This leaves either shunt or V/Q mismatch, which can be distinguished with response to O_2 (absence of response suggests shunt. V/Q mismatch should respond to O_2)
4. If high $PaCO_2$, then hypoventilation is present. Check A-a gradient to determine if co-existing shunt or V/Q mismatch (presence of A-a gradient suggests yes and should check response to O_2 to distinguish between these two possibilities)

ALVEOLAR-ARTERIAL (A-a) O_2 GRADIENT

- **NORMAL**—A-a gradient < age/4 + 4, or <0.4 × age. Usually <15 mmHg in young, up to ~30 mmHg in elderly

DIAGNOSTIC ISSUES (CONT'D)

- **CALCULATION**—A-a gradient = P_AO_2 – P_aO_2 = $[(P_B–47) \times 0.21– PaCO_2/0.8] – P_aO_2$, where P_B = barometric pressure ≈760 mmHg if at sea level
- **INTERPRETATION**—calculation used when FiO_2 is 21% (room air). Normal range changes with supplemental oxygen. If A-a gradient normal, consider hypoventilation or low inspired O_2 as causes of hypoxemia. If A-a gradient high, consider V/Q mismatch, R to L shunt, and/or diffusion defects

P_aO_2/P_AO_2 RATIO

—when FiO_2 >21% (i.e. on supplemental O_2 therapy), P_aO_2/P_AO_2 ratio should be used instead of A-a gradient

- **NORMAL**—P_aO_2/P_AO_2 ≥0.99 – (0.003 × age), usually >0.82
- **INTERPRETATION**—unlike A-a gradient, P_aO_2/P_AO_2 ratio decreases in the presence of V/Q mismatch, R to L shunt, or diffusion defects

MANAGEMENT

ACUTE—ABC, **O_2**, IV, **mechanical ventilation if severe respiratory failure** (invasive or non-invasive)

TREAT UNDERLYING CAUSE

TREATMENT ISSUES

AVOID OVER-CORRECTING O_2 SATURATION IN HYPOVENTILATION—O_2 displaces CO_2 from Hb, causing elevated CO_2 in blood. In addition, O_2 may change V/Q relationship and may decrease hypoxic drive. For patients with chronic hypoventilation (↑ HCO_3), O_2 to keep saturation between 88 and 92% only

SPECIFIC ENTITIES

HYPOXEMIC RESPIRATORY FAILURE (P_aO_2 < 50 mmHg even with F_IO_2 > 50)—failure to oxygenate, see DIFFERENTIAL DIAGNOSIS OF HYPOXEMIA

HYPERCARBIC RESPIRATORY FAILURE (P_aCO_2 greater than baseline with concomitant acidosis)—failure to ventilate, see hypoventilation under DIFFERENTIAL DIAGNOSIS OF HYPOXEMIA

Acute Respiratory Distress Syndrome

DIFFERENTIAL DIAGNOSIS

PULMONARY EDEMA

- **CARDIOGENIC**—ischemic cardiomyopathy, valvular disease
- **NON-CARDIOGENIC**—ARDS, toxic inhalation, drug reaction, aspiration, fat embolism

INFECTION—bacterial, viral, mycobacterial, fungal

HEMORRHAGE—pulmonary embolism, pulmonary contusion, bleeding diathesis, DIC, anticoagulation, vasculitis (granulomatosis with polyangiitis, Goodpasture's, SLE)

PATHOPHYSIOLOGY

DEFINITION OF ARDS (Berlin Definition, JAMA 2012 307:23)

- **ACUTE ONSET**—new (or worsening) respiratory symptoms <1 week
- **BILATERAL ALVEOLAR INFILTRATES**—usually asymmetric/patchy, peripheral > central
- **MODERATE TO SEVERE HYPOXEMIA (WITH PEEP OR CPAP ≥5 cmH_2O)**—mild: $PaO_2/FiO_2 > 200$ mmHg but ≤300 mmHg; moderate: PaO_2/FiO_2 100–200 mmHg; severe: $PaO_2/FiO_2 \leq 100$ mmHg
- **ABSENCE OF CARDIAC FAILURE OR FLUID OVERLOAD**—objective assessment to exclude hydrostatic pulmonary edema (e.g. echocardiography) required if no risk factors for ARDS present

INFLAMMATION IN ARDS—ARDS is a clinical syndrome of severe lung injury due to systemic inflammation. Cytokine release results in capillary membrane permeability and protein-rich fluid exudation into the alveolar space, impairing oxygenation. Ongoing inflammation may lead to extensive fibrosis

PHASES OF ARDS—<10 days = exudative phase, 10–14 days = fibroproliferative/fibrotic phase

HYPOXEMIA IN ARDS—caused mainly by right to left shunt, thus the P_aO_2/F_IO_2 ratio is low. V/Q mismatch and hypoventilation may also contribute

CAUSES—over 80% of ARDS caused by infection, aspiration, and trauma

- **PULMONARY**—pneumonia (bacterial, viral, fungal including PJP, mycobacterial), aspiration, drowning, inhalation injury (O_2, smoke, NO_2), reperfusion injury (post-lung transplant or cardiopulmonary bypass)
- **GI**—acute pancreatitis
- **CNS**—neurogenic (intracerebral hemorrhage)

PATHOPHYSIOLOGY (CONT'D)

- **SYSTEMIC**—sepsis, transfusion reaction, major trauma, drugs (heroine, cocaine, aspirin, chemotherapy)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, troponin/CK, urinalysis, lactate
- **MICROBIOLOGY**—blood C&S, sputum Gram stain/C&S/AFB, urine C&S
- **IMAGING**—CXR, CT chest, echocardiogram
- **ABG**
- **ECG**
- **PULMONARY ARTERY CATHETERIZATION**

DIAGNOSTIC AND PROGNOSTIC ISSUES

PROGNOSIS OF ARDS—overall mortality rate ~45%. Mortality increases with additional organ failure (>99% if three system failures)

MANAGEMENT

ABC—O_2 to keep S_pO_2 85–95%, IV access

MECHANICAL VENTILATION

- **LUNG-PROTECTIVE VENTILATION** (low tidal volumes to minimize ventilation-induced lung injury)—set tidal volume ~4–8 mL/kg, based on ideal body weight, maintain plateau pressure ≤30 cmH_2O
- **PEEP**—should be employed to keep FiO_2 in presumed non-toxic range (<0.60). Increase PEEP by increments of 3–5 cm (maximum = 15–20 cm) to ↑ mean airway pressure, recruit alveoli (preventing alveolar collapse and ventilator-induced lung injury) and ↑ functional residual capacity (may be harmful)
- **RECRUITMENT**—recruitment maneuvers may be used to keep alveoli open; e.g. 40 cmH_2O PEEP for 40 s
- **PERMISSIVE HYPERCAPNIA**—generally tolerate pH >7.25, may need to run HCO_3 infusion to maintain pH
- **SALVAGE/ALTERNATE MODES OF VENTILATION**—APRV (airway pressure release ventilation), HFOV (high-frequency oscillatory ventilation), prone positioning (only salvage technique with mortality benefit; **NEJM 2013 368:23**)

MEDICATIONS—no effective pharmacologic therapy for ARDS. There is limited evidence regarding **steroid** use for treatment of ARDS and no evidence for prophylaxis. Some clinicians still

MANAGEMENT (CONT'D)

use in non-resolving cases (start 7–14 days after onset. *Methylprednisolone* 2 mg/kg load, then 2 mg/kg/day from days 1 to 14, then taper by 50%/week to 0.125 mg/kg/day, monitor for infection). Inhaled nitric oxide or epoprostenol (Flolan) selectively dilate pulmonary vessels of ventilated alveoli, improving V/Q matching. Reduce pulmonary artery pressures and intrapulmonary shunting with an increase in P_aO_2/F_IO_2

TREAT UNDERLYING CAUSE

Ventilation Issues

MECHANICAL VENTILATION

INDICATIONS FOR MECHANICAL VENTILATION

- **DECREASED COMPLIANCE** (stiff lungs)—pulmonary fibrosis, pulmonary edema, ARDS
- **INCREASED RESISTANCE** (narrowed airways, air trapping)—status asthmaticus, COPD exacerbations, bronchial tumor, excessive secretions
- **MECHANICAL FAILURE**—spinal cord injury, Guillain–Barré
- **LACK OF RESPIRATORY DRIVE**—neurologic disease, drug overdose

NON-INVASIVE POSITIVE PRESSURE VENTILATION (NIPPV)

- **CONDITIONS IN WHICH NIPPV IS USED**—COPD, HF, asthma, postoperative respiratory failure, postextubation in select situations. If no improvement after 30 min-1 h, should intubate
- **INDICATIONS**—pH 7.2–7.3, RR >25, use of accessory muscles, and cooperative
- **CONTRAINDICATIONS**—↓ level of consciousness (but possible use if due to ↑ PCO_2), respiratory arrest, facial trauma/surgery/burn, upper airway obstruction, copious secretions, aspiration risk, GI bleeding, gastroesophageal surgery, esophageal rupture, hemodynamic instability, co-existent organ failure, massive obesity, extreme anxiety
- **MASK TYPES**—full face, nose and mouth, nasal only
- **VENTILATORY MODES**—CPAP or BIPAP. CPAP is mainly used for obstructive sleep apnea; however, can be used in isolated hypoxemia (ventilation adequate). BIPAP is used to assist with oxygenation and ventilation

INVASIVE MECHANICAL VENTILATION

- **INDICATIONS**—severe hypoxemia, acute hypercapnia, need for airway protection (GCS ≤8), impending airway occlusion, therapeutic hyperventilation. In general, intubate if BIPAP contraindicated or failed, or clinical status severe and likely require longer term ventilation
- **TUBES**—endotracheal tubes, tracheostomy tubes (see ARTIFICIAL AIRWAYS)

MECHANICAL VENTILATION (CONT'D)

TERMINOLOGY

- **RESISTANCE**—restriction that inhibits flow of gas in airways. May result in increased P_{peak} or decreased V_e
- **COMPLIANCE**—ease with which lungs expand. Normal ~50 mL/cm H_2O
- **TIDAL VOLUME** (VT)—amount of air delivered per breath. Normal ~8 mL/kg (500 mL)
- **MINUTE VOLUME** (Ve)—amount of air delivered per minute. Ve (mL/min) = VT × RR
- **POSITIVE END-EXPIRATORY PRESSURE** (PEEP)—maintenance of positive pressure throughout exhalation. PEEP improves P_aO_2 mainly by augmenting mean airway pressure. Other potential mechanisms include recruitment of collapsed alveoli, increased functional residual capacity, and improvement in V/Q matching. Usually set at 5–15 cmH_2O. >15 cmH_2O may cause barotrauma
- **PEAK AIRWAY PRESSURE** (P_{peak})—maximal inspiratory pressure to distend alveoli and to overcome airway resistance. P_{peak} is dependent on inflation volume, airways resistance, and lung/chest wall compliance. Happens about halfway through inspiration phase
- **PLATEAU PRESSURE** (P_{plat})—pressure to prevent lungs from deflating at end inspiration. Related to lung/chest wall compliance. Limit to ≤30 cmH_2O in ARDS
- **RAPID SHALLOW BREATHING INDEX** (RSBI)—index used for weaning/liberation. The lower the better (<70 is excellent, <100 is good). RSBI = RR/tidal volume (measured in liters)

ASSESSMENT OF AIRWAY

PRIOR TO INTUBATION—assess airway to anticipate difficulty of procedure, establish IV access (for blood pressure control and medication administration), position patient (sniffing position), remove false teeth/dentures, suction and endotracheal tube ready

ASSESSMENT OF AIRWAY (CONT'D)

SUBJECTIVE SIGNS OF DIFFICULT AIRWAY—prominent upper incisors, short/thick neck, large tongue, micrognathia

OBJECTIVE SIGNS OF DIFFICULT AIRWAY

- **NECK EXTENSION**—atlanto-occipital extension ≤35°
- **THYROMENTAL DISTANCE**—<6 cm [<2.4 in] (3 finger breaths)
- **MOUTH OPENING**—<4 cm [<1.6 in] (2–3 finger breaths)
- **MANDIBULAR LENGTH**—<9 cm [3.5 in]
- **MALLAMPATI SCORE**—III/IV may indicate difficult airway for intubation
  - **I** = visualization of the soft palate, fauces, uvula, anterior and posterior pillars
  - **II** = visualization of the soft palate, fauces, and uvula
  - **III** = visualization of the soft palate and the base of the uvula
  - **IV** = soft palate is not visible at all

ARTIFICIAL AIRWAYS

ORAL AIRWAYS—used in unconscious patients without a gag reflex to prevent airway collapse/obstruction. Also allow access for suctioning and stimulation of cough. Sizes 8, 9, 10 cm in length (Guedel sizes 3, 4, 5). Insert backward along the hard palate and rotate into position. If improperly placed, may push tongue posteriorly and obstruct the airway. Can induce vomiting or laryngospasm if placed in an awake or semiconscious patient

ENDOTRACHEAL TUBES (NEJM 2007 356:e15)—inserted nasally or orally, with aid of laryngoscope, bronchoscope, or glidescope. Sizes 6.0–9.0 mm in diameter. Cuff occludes airway surrounding endotracheal tube (cuff pressure <25 mmHg ideally; inflate cuff only to the point when leak disappears, i.e. use minimal occlusion pressure to avoid iatrogenic airway ischemia)

TRACHEOSTOMY TUBES

- **INDICATIONS**—long-term ventilation (>10–14 days intubation), to facilitate weaning, or to bypass an upper airway obstruction
- **TYPES**—Portex, Shiley (fenestrated)
- **COMPONENTS**—fenestrations (openings in tracheostomy tube allowing weaker patients to tolerate plugging trials easier), disposable inner cannula (seal fenestration, allows easier exchange of tracheostomy tube if plugged), cuff (balloon that occludes airway surrounding tracheostomy tube)
- **PLUGGING PROCEDURE**—provide alternate source of O_2 (via upper airway), suction of upper and lower airways, deflate cuff completely, remove inner cannula if present, insert plug and lock it in place, assess patient for airway patency, increased work of breathing and stridor
- **DECANNULATION CRITERIA**—breathing spontaneously without ventilator assistance, consistent cough and ability to expectorate secretions, airway protected, on minimal F_iO_2 (<40% or <5–6 l/min), no evidence of upper airway obstruction

TRACHEOSTOMY BUTTONS—to maintain stoma during weaning. Less resistance than plugged tracheostomy tube. Usually left in for <24 h

VENTILATORY SETTINGS

RATE—minimal respiratory rate. Normal = 8–16

TIDAL VOLUME—range 5–8 mL/kg of ideal body weight. Normal = 400–600 mL. In volume cycled modes only

PEAK FLOW—determines how fast a positive pressure breath is delivered. In volume cycled modes only

PRESSURE SUPPORT—ranges from 6 cm H_2O (almost no support) to 30 cm H_2O (max). Normal = 14–16 cm H_2O. In pressure limited modes only

INSPIRATORY TIME—determines duration over which the pressure is delivered. In pressure limited modes only

F_iO_2—range 0.21–1.0. Normal = 0.4 or to keep S_pO_2 ≥92%

SENSITIVITY—determines the degree of patient effort required to trigger a positive pressure breath

PEEP/EPAP—generally start at 5 cm H_2O, max 15–20 cm H_2O (usually in ARDS)

VENTILATORY MODES

- **ASSIST CONTROL** (AC)—mandatory ventilator controlled breaths at set rate. Patient may breathe spontaneously (i.e. trigger the ventilator, "assist" breaths) but ventilator augments breath to reach fixed volume or pressure (VC or PC)
- **VOLUME CONTROL** (VC)—set tidal volume, machine-initiated inspiration
- **PRESSURE CONTROL** (PC)—set pressure, machine-initiated inspiration
- **VOLUME SUPPORT** (VS)—set tidal volume, patient-initiated inspiration (no backup rate, ventilator only boosts airflow to predetermined volume)

VENTILATORY SETTINGS (CONT'D)

- **PRESSURE SUPPORT** (PS)—set pressure, patient-initiated inspiration (no backup rate, ventilator only boosts airflow to pre-determined pressure)
- **SYNCHRONIZED INTERMITTENT MANDATORY VENTILATION** (SIMV)—mandatory positive pressure breaths delivered at a preset rate and breath type (either volume cycled or pressure limited). Any other breaths patient takes are normal spontaneous breaths with or without additional pressure/volume support (i.e. patient determines size of breath)
- **PRESSURE-REGULATED VOLUME CONTROL** (PRVC)—similar to volume control ventilation, with the ventilator monitoring all respiratory parameters (e.g. pressure) to continually maintain the set tidal volume
- **AIRWAY PRESSURE RELEASE VENTILATION** (APRV)—a form of inverse ratio ventilation using two levels of CPAP (P_{high} and P_{low}). This mode attempts to maximize mean airway pressure and thus alveolar recruitment at P_{high}, while dropping briefly to P_{low} for CO_2 elimination. Used in refractory hypoxemia due to ARDS or massive atelectasis
- **HIGH FREQUENCY OSCILLATORY VENTILATION** (HFOV)—employs very high respiratory rates and very small tidal volumes. Goal is to maximize alveolar recruitment and to minimize ventilator induced lung injury. Often used in patients with refractory hypoxemia due to ARDS who fail conventional ventilation
- **CONTINUOUS POSITIVE AIRWAY PRESSURE** (CPAP)—allows a spontaneously breathing patient to breathe at an elevated baseline airway pressure, permitting improved ventilation, decreased work of breathing, reduced atelectasis, and improved gas exchange. May be used as NIPPV (more common) or in intubated patients (generally referred to as PEEP with invasive ventilation)
- **BILEVEL POSITIVE AIRWAY PRESSURE** (BIPAP)—consists of inspiratory positive airway pressure phase (IPAP, start at 12 cmH_2O, up to 20 cmH_2O) and expiratory positive airway pressure phase (EPAP, start at 6 cmH_2O, up to 10 cmH_2O). IPAP leads to ↑ airflow which ↑ Ve and helps to ↓ PCO_2, whereas EPAP leads to ↑ FRC and mainly ↑ PO_2. May be used in NIPPV (more common) or intubated patients

VENTILATOR WEANING AND LIBERATION

CRITERIA FOR LIBERATION FROM VENTILATOR

- **REVERSAL OF INITIAL DISEASE PROCESS**—complete reversal not necessary. Ideally, stable chest wall and good pain control. Minimal secretions, minimal sedation, no metabolic acidosis, clear CXR, adequate hemoglobin, adequate nutrition
- **F_IO_2**—effective oxygenation at $F_IO_2 \leq 0.5$
- **PEEP**—effective gas exchange at PEEP ≤7.5 cmH_2O (unless required for triggering e.g. in advanced COPD)
- **MINUTE VENTILATION**—maintain normal pH at Ve 10–12 Lpm or less
- **SPONTANEOUS PARAMETERS**—while off ventilator, able to generate own parameters. VT >5–7 mL/kg, Ve <10 L, VC = 12–15 mL/kg, NIF (negative inspiratory force) >−20 cmH_2O, RSBI <105 (even better if <70)

PROCESS FOR WEANING VENTILATED PATIENTS

- **MEASURES**—PSV trial builds endurance. Cold nebulizer trial builds strength. The less time the patient is on ventilator, the more normal their lung function, the simpler and shorter the weaning process. Daily spontaneous breathing trials significantly shorten the weaning process
- **QUICK**—switch directly to CPAP, cold neb, or bagger trial. Extubate soon after
- **SLOW**—PSV maximum and slowly decreasing to minimal levels, intermittent trials of PSV, CPAP, or cold neb allowing patient to rest on increased or full support

VENTILATOR-ASSOCIATED PNEUMONIA

PATHOPHYSIOLOGY

- **DEFINITION**—pneumonia in patient mechanically ventilated ≥48 h
- **RISK FACTORS**—prolonged mechanical ventilation, need for reintubation, aspiration of gastric contents, acid suppression therapy, supine positioning, poor oral/dental hygiene
- **MICROBIOLOGY**—predominantly *S. aureus* (including MRSA), Enterobacteriaceae, *Pseudomonas aeruginosa*. Other common microorganisms include *Stenotrophomonas*, *Acinetobacter*, anaerobes

DIAGNOSIS—diagnosis can be difficult. Clinical scores can be used to aid in diagnosis

VENTILATOR-ASSOCIATED PNEUMONIA (CONT'D)

TREATMENTS

- **EMPIRIC THERAPY**—anti-pseudomonal carbapenem or β-lactam/β-lactamase inhibitor *plus* aminoglycoside or respiratory fluoroquinolone. Add vancomycin or linezolid if high rates of MRSA (linezolid may have better lung penetration). De-escalate therapy as soon as possible when culture results known
- **DURATION OF THERAPY**—depends on the microorganism, severity of infection, patient comorbidities and response to therapy, but short courses generally adequate (7–8 days) except for *Pseudomonas aeruginosa* (14 days)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE VENTILATOR-ASSOCIATED PNEUMONIA?

	LR+	LR–
Physical and investigations		
Fever	1.2	0.86
Leukocytosis	1.3	0.74
Purulent sputum	1.3	0.63
≥2 of fever/↑ WBC/purulent sputum	2.8	0.41
Crepitation on auscultation	1.2	0.68
Hypoxemia	1.1	0.91
Radiographic features		
New infiltrate on radiograph	1.7	0.35
Air bronchogram	3.8	0.29
Silhouette sign	1.2	0.63
Alveolar infiltrate	1.2	0.47
Fissure abutment	1.9	1.0
Atelectasis	0.77	1.1
Pulmonary secretion analysis		
>50% neutrophils	2	0.09
Intracellular (PMN) bacteria	1.0	1.0
Positive Gram stain		
Blind bronchial aspirate	2.1	0.60
Mini-BAL fluid	5.3	0.5
BAL fluid	18	0.56
Culture		
Blind bronchial asp. ($>10^5$ CFU/mL)	9.6	0.42
BAL fluid ($>10^4$ CFU/mL)	1.4	0.78
Clinical pulmonary infection score		
Score >6	2.1	0.38

APPROACH—"while no single sign is diagnostic of VAP, the appearance of a new infiltrate on CXR should prompt one to check for fever, purulent sputum and leukocytosis (VAP becomes more likely when 2 or more of these signs are positive). Analysis of pulmonary secretions can further refine the diagnosis of VAP. The absence of CXR infiltrate moderately decreases the chance of VAP"

JAMA 2007 297:14

Shock

DIFFERENTIAL DIAGNOSIS

★SHOCK★

SEPTIC—pneumonia, bacteremia/line infection, UTI, intraabdominal infection, meningitis, necrotizing fasciitis

HYPOVOLEMIC/HEMORRHAGIC—blood loss (trauma, GI bleed, retroperitoneal hemorrhage), GI losses, renal losses, burns

OBSTRUCTIVE—pulmonary embolism, tension pneumothorax, cardiac tamponade

CARDIOGENIC—ischemic, hypertensive, valvular, arrhythmia, peripartum, toxic, infiltrative, idiopathic, familial, autoimmune

KLASSIFIED CAUSES

- **MEDICATIONS**—antihypertensives, AV nodal blocking agents
- **ANAPHYLACTIC**

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **LIVER**—hepatic failure
- **ENDOCRINE**—adrenal insufficiency, myxedema
- **SPINAL**—cord compression/transection

PATHOPHYSIOLOGY

DEFINITION—hypotension leading to cellular hypoperfusion, hypoxia, lactic acidosis, and subsequent organ failure (oliguria, hepatic and GI dysfunction, altered mental status)

IT'S SIMPLE MATH

- **BP** = CO × SVR = (SV × HR) × SVR, where CO = cardiac output and HR = heart rate
- **STROKE VOLUME** (SV)—decreases in cardiogenic, hypovolemic, adrenal, hypothyroidism, and obstructive shock

PATHOPHYSIOLOGY (CONT'D)

- **SYSTEMIC VASCULAR RESISTANCE** (SVR)—decreases in distributive shock (septic, anaphylactic, neurogenic, hepatic)

CLINICAL FEATURES

HISTORY—pay particular attention to risk factors for sepsis, blood loss, MI, or pulmonary embolism; past medical history; medications

PHYSICAL—vitals. Assess volume status, cardiac and respiratory function, and extremities. Look for evidence of end-organ dysfunction

ASSESSMENT OF VOLUME STATUS

- **VITALS**—postural heart rate and blood pressure
- **SKIN**—skin turgor (inner aspect of thigh, sternum), oral mucosa
- **CARDIOPULMONARY**—JVP or CVP, crackles, S_3
- **URINE**—urine output
- **EXTREMITIES**—peripheral pulses, skin temperature, capillary refill

FEET EXAMINATION

- **WARM FEET**—vasodilation → distributive shock → give fluids and consider vasopressors
- **COLD FEET**—vasoconstriction → cardiogenic vs. hypovolemic/obstructive vs. late septic shock → give fluids and consider inotropes especially if suspect cardiogenic cause. Also check troponin and consider echocardiogram

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, INR, PTT, AST, ALT, ALP, bilirubin, Ca, Mg, PO_4, TSH, D-dimer, lactate, CK, troponin, urinalysis, random cortisol
- **MICROBIOLOGY**—blood C&S, sputum C&S, urine C&S
- **IMAGING**—depends on suspected source; CXR, AXR, echocardiogram, CT where appropriate (e.g. CT abdomen if intra-abdominal source suspected)
- **ECG**
- **ABG**

DIAGNOSTIC ISSUES

PULMONARY ARTERY CATHETERIZATION

- **INDICATIONS**—diagnosis (shock states, primary pulmonary hypertension, valvular disease, intracardiac shunts, cardiac tamponade, pulmonary embolus), hemodynamic monitoring (complicated AMI, multi-organ system failure, post-cardiac surgery), treatment (aspiration of air emboli). No mortality difference with use of PA catheter
- **CONTRAINDICATIONS**—tricuspid or pulmonary mechanical valve, tricuspid or pulmonary valve endocarditis, right heart mass (thrombus and/or tumor)
- **SITES OF ENTRY** (relative preference)—right internal jugular vein (has shortest and straightest path to the heart) > left subclavian vein > right subclavian vein > left internal jugular vein > femoral veins
- **NORMAL VALUES**
  - **CENTRAL VENOUS PRESSURE** (CVP) = 5–8 mmHg, may accept higher values in patients ventilated with high PEEP or high baseline LVEDP (e.g. chronic hypertension)
  - **RIGHT ATRIAL PRESSURE** (RAP) = 5–8 mmHg
  - **RIGHT VENTRICULAR PRESSURE** (RVP) = 20–30/2–8 mmHg
  - **PULMONARY ARTERY PRESSURE** (PAP) = 20–30/5–15 mmHg, mean 10–22 mmHg
  - **PULMONARY CAPILLARY WEDGE PRESSURE** (PCWP) = pulmonary artery occlusion pressure (PAOP) ~ LA pressure = 8–12 mmHg (PCWP >18 mmHg suggests interstitial edema, PCWP >24 mmHg suggests alveolar edema)
  - **LEFT VENTRICULAR PRESSURE** (LVP) = 120/8 mmHg
  - **AORTIC PRESSURE** = 120/80 mmHg, MAP 70–110 mmHg
  - **SYSTEMIC VASCULAR RESISTANCE INDEX** (SVRI) = 900–1,200 dyn/s/cm^2
  - **CARDIAC INDEX** = 2.4–4.2 L/min/m^2, CO = 4–7 L/min
  - **DO_2** = 400–650 mL/min/m^2
  - **VO_2** = 125–175 mL/min/m^2
  - **COMPLICATIONS**—arterial puncture, hemothorax, pneumothorax, venous or air embolus, sustained ventricular tachycardia, ventricular fibrillation, heart block (most commonly RBBB, or complete heart block in the setting of pre-existing LBBB), infection, pulmonary artery thrombosis/embolism/infarction/rupture, knotting of catheter (requires fluoroscopic removal), pulmonary or tricuspid valve insufficiency

DIAGNOSTIC ISSUES (CONT'D)

DISTINGUISHING FEATURES BETWEEN SHOCK STATES

	CO	CVP	PCWP	SVR
Distributive	↑	↓/N	↓/N	↓
Hypovolemic	↓	↓	↓	↑
Cardiogenic	↓	↑	↑	↑
Isolated RHF	↓	↑	↓	↑
Isolated LHF	↓	↓/N	↑	↑
Tamponade[a]	↓	↑	↑	↑

[a]In tamponade or tension pneumothorax, observe equalization of pressures, i.e. CVP = RA = RV–EDP = PCWP; cardiogenic shock gives heart failure picture on CXR, whereas tamponade usually has clear CXR with cardiomegaly only

Related Topics
Anaphylaxis (p. 423)
Myocardial Infarction (p. 28)
Sepsis (p. 111)
Tamponade (p. 35)

MANAGEMENT

ACUTE—ABC, $\mathbf{O_2}$, cardiac and oximetry monitoring, **IV fluid resuscitation** (1–5 L), **ICU consult**, consider intubation/mechanical ventilation, **inotropes/vasopressors** (*Norepinephrine* 1–30 µg/min IV. *Vasopressin* 0.01–0.04 U/min IV. *Epinephrine* 1–20 µg/min IV. *Ephedrine* 5–25 mg IV q5–10 min until blood pressure stable. *Phenylephrine* 20–200 µg/min IV. *Dobutamine* 2.5–15 µg/kg/min IV. *Milrinone* 0.375–0.75 µg/kg/min IV. *Dopamine* start 1–4 µg/kg/min IV, titrate to maximum 20 µg/kg/min. *Midodrine* 5–10 mg PO TID). **Correct coagulopathy** (transfuse PRBC, FFP, cryoprecipitate)
TREAT UNDERLYING CAUSE

TREATMENT ISSUES

INOTROPES/VASOPRESSORS

- **PHYSIOLOGY**—α1 = peripheral vasoconstriction = ↑ peripheral vascular resistance = treatment for sepsis; β1 = inotropic and chronotropic effect = ↑ cardiac output = treatment for heart failure; β2 = peripheral vasodilation = counter α1 effect

Agent	Mechanism of action	Special note
Norepinephrine	α1 mainly, β1 → ↑ PVR, ↑ CO	First line for septic shock
Vasopressin	V1, V2 → dilates renal, pulmonary, cerebral,coronary arteries and constricts others	Second line for sepsis; AE: Gut ischemia, skin necrosis
Epinephrine	β1, β2, α1 → ↑ CO, ↑ PVR	Salvage for sepsis, first line for anaphylaxis; AE: ischemia
Phenylephrine	α1 → ↑ PVR	Sepsis, counteract spinal/epidural anesthesia
Ephedrine	β1, β2, α1 → ↑ CO, ↑ PVR	Bolus therapy pending CVC placement for continuous vasopressor therapy
Dobutamine	β1, β2, → ↑ CO, ↓ PVR	First line for cardiogenic shock
Milrinone	Phosphodiesterase inhibitor → ↑ CO, ↓ PVR	First line for cardiogenic shock with pulmonary HTN
Dopamine 1–2 µg/kg/min	DA → dilates renal, mesenteric, cerebral arteries and airways	↑ renal perfusion/GFR (controversial)
Dopamine 5–10 µg/kg/min	DA, β1 → ↑ CO	HF/sepsis; AE: tachycardia
Dopamine >10 µg/kg/min	α1 → ↑ PVR	Sepsis/HF; AE: tachycardia
Midodrine	α1 → ↑ PVR	Sepsis; oral

where *AE* adverse effects, *CO* cardiac output, *CVC* central venous catheter, *DA* dopamine, *HF* heart failure, *HTN* hypertension, *PVR* peripheral vascular resistance

Sepsis and Septic Shock

NEJM 2006 355:16
Surviving Sepsis Campaign Guidelines Crit Care Med 2013 41:2

PATHOPHYSIOLOGY

DEFINITIONS

- **SIRS**— ≥2 of temperature >38.3 °C [>100.9 °F] or <36 °C [<96.8 °F], heart rate >90 beats min, respiratory rate >20 or P_aCO_2 < 32 mmHg, WBC $>12\times10^9$/L or $<4\times10^9$/L or >10% bands
- **SEPSIS**—SIRS plus documented or suspected infection
- **SEVERE SEPSIS**—sepsis-associated hypoperfusion leading to lactic acidosis, oliguria, or acute alteration of mental status (i.e. sepsis plus organ dysfunction)
- **SEPTIC SHOCK**—sepsis-induced hypotension (i.e. SBP <90 mmHg) despite adequate fluid resuscitation or vasopressor dependence

SIMPLIFIED MECHANISM OF INJURY—infection → systemic inflammation (SIRS) → complement activation, ↓ fibrinolysis → endothelial dysfunction, microvascular coagulopathy and thrombosis → organ failure. Too little or too much host response

MECHANISM OF ACUTE KIDNEY INJURY IN SEPSIS

1. Hypotension, increased catecholamines and vasopressor resistance to norepinephrine and angiotensin II → renal ischemia → acute kidney injury
2. Hyperglycemia → white cell dysfunction and inflammation → acute kidney injury
3. Disseminated microvascular coagulation → glomerular and vascular microthrombosis → acute kidney injury

BAND CELLS—neutrophils with unsegmented nuclei, a developmental stage immediately preceding the mature segmented form

- **LEFT SHIFT**—band cell count $>0.7\times10^9$/L, commonly seen in infections
- **"SEVERE" LEFT SHIFT**—cells as immature as metamyelocytes may be seen in left shift in response to infection, but unusual to see more immature cells (myelocytes, promyelocytes, blasts). When present, suggestive of myeloproliferative disorder (chronic myelogenous leukemia, agnogenic myeloid metaplasia, or one of the various forms of acute leukemia)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, albumin, troponin, CK, INR, PTT, lactate, urinalysis, random cortisol
- **MICROBIOLOGY**—blood C&S, sputum Gram stain/AFB/C&S, urine C&S, other based on clinical syndrome (e.g. peritoneal, pleural, cerebrospinal fluid C&S)
- **IMAGING**—CXR
- **ABG**

SPECIAL

- **$ScvO_2$ MONITORING**—with internal jugular or subclavian central line insertion
- **LUMBAR PUNCTURE**—if altered level of consciousness
- **THORACENTESIS**—if significant pleural effusion(s)
- **PARACENTESIS**—if ascites

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS ADULT PATIENT WITH SUSPECTED BACTEREMIA REQUIRE BLOOD CULTURES?

	LR+	LR–
Chills in febrile patients	2.2	0.56
Shaking chills	4.7	–
Subjective fever	1.0	0.95
Temperature ≥38.0 °C	1.9	0.54
High clinical impression (≥50% probability of bacteremia)	2.3	–
Intermediate clinical impression (10–49%)	0.49	–
Low clinical impression (≤10%)	0.48	–
Systemic inflammatory response syndrome (SIRS)	1.8	0.09
Shapiro clinical decision rule	1.3	0.08

Shapiro Decision Rule: blood cultures indicated if 1 major OR 2 minor criteria. Major criteria (suspicion of endocarditis, temperature >39.4 °C, indwelling catheter), minor criteria (temperature 38.3–39.3 °C, age >65 years, chills, vomiting, SBP < 90 mmHg, WBC >18,000/μL, creatinine >177 μmol/L

APPROACH—pretest probability of true positive blood cultures is low (4.1–7.3%), but

INVESTIGATIONS (CONT'D)

depends on the clinical context (low risk: cellulitis, community acquired pneumonia; intermediate risk: pyelonephritis; high risk: severe sepsis, acute bacterial meningitis, septic shock). Blood cultures should not be ordered for isolated fever/leukocytosis. The Shapiro decision rule may identify low-risk patients not requiring further investigation. These findings do not apply if there is a suspicion for endocarditis or in immunocompromised patients

JAMA 2012 308:5

MANAGEMENT

ACUTE—ABC, $\mathbf{O_2}$, IV, consider intubation/mechanical ventilation

RESUSCITATION (early goal-directed therapy)—**fluids** (Plasmalyte or Ringer's lactate 3–10 L IV, consider colloids such as PRBC and albumin, avoid hydroxyethyl starches) and **vasopressors/inotropes** (*norepinephrine* 1–30 mcg/min IV, *vasopressin* 0.01–0.04 U/min IV, *dobutamine* 2.5–15 μg/kg/min IV) during first 6 h to maintain CVP 8–12 mmHg, MAP ≥65 mmHg or SBP >90 mmHg, urine output ≥0.5 mL/kg/h and central venous or mixed venous saturation ≥70%

NEJM 2001 345:19

ANTIMICROBIALS—early **empiric antimicrobials should be administered ASAP, order STAT**. If suspect pulmonary source, macrolide plus β-lactam for community-acquired pneumonia, anti-pseudomonal plus aminoglycoside or fluoroquinolone ± vancomycin (if high-level MRSA endemicity) for nosocomial pneumonia. If suspect urinary source, third-generation cephalosporin or aminoglycoside. If suspect intra-abdominal source, β-lactam/β-lactamase inhibitor or carbapenem. **Tailor antimicrobials** once organism(s) identified. Know your local epidemiology

SOURCE CONTROL—absolutely imperative. Must drain abscesses and debride devitalized tissues to achieve source control

GLYCEMIC CONTROL—**insulin infusion** to keep serum glucose <10 mmol/L [<180 mg/dL], maintaining euglycemia *may* improve outcomes; however, must avoid hypoglycemia

STEROIDS—controversial as no reduction in mortality but hasten time to shock reversal, administer ***hydrocortisone*** 50 mg IV q6h in patients with vasopressor-dependent shock

BLOOD PRODUCTS—in septic shock patients with low $S_{cv}O_2$ during the first 6 h of resuscitation target hematocrit should be 30%. In stable patients, the threshold for transfusion should be hemoglobin <70 g/L, with a target of 70–90 g/L

PROPHYLAXIS—**DVT** (unfractionated heparin SC, LMWH, fondaparinux, pneumatic stockings), **stress ulcer** (*ranitidine* 50 mg IV q8h or 150 mg PO/NG q12h)

SPECIFICS—**ARDS** (lung-protective ventilation), **acute kidney injury** (avoid nephrotoxins, supportive renal replacement therapy), **early enteral feeding**

Lactic Acidosis

DIFFERENTIAL DIAGNOSIS

TYPE A (OCCURS WITH POOR TISSUE PERFUSION OR OXYGENATION)

- **TISSUE HYPOXIA**—shock, reduced cardiac output or cardiac arrest, hypoxemia, anemia, carbon monoxide poisoning, methemoglobinemia
- **INCREASED OXYGEN DEMAND**—sepsis, seizures, exercise

TYPE B (WHEN EVIDENCE OF POOR TISSUE PERFUSION OR OXYGENATION IS ABSENT)

- **B1** (systemic diseases)—renal and hepatic failure, diabetes mellitus, and malignancy (lymphoma, leukemia, small cell carcinoma)
- **B2** (drugs/toxins)—metformin, alcohols (ethanol, methanol, ethylene glycol, paraldehyde), cyanide, nitroprusside, isoniazid, epinephrine

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **B3** (inborn errors of metabolism)—defects of pyruvate metabolism, defects of NADH oxidation, disorders of gluconeogenesis (type 1 glycogen storage disease), fatty acid oxidation defects, defects of organic acid metabolism

PATHOPHYSIOLOGY

DEFINITION—>4 mmol/L [>36 mg/dL] (normal ~1 mmol/L [9 mg/dL]) + metabolic acidosis

LACTIC ACID PRODUCTION—part of the glycolytic pathway as pyruvate is converted to lactate to generate NAD from NADH. As anaerobic metabolism increases (↓ O_2 delivery, ↑ metabolic rate), lactate accumulates and causes metabolic acidosis

PATHOPHYSIOLOGY (CONT'D)

LACTIC ACID METABOLISM—lactate is metabolized by the liver. Alteration of hepatic function could cause some degree of lactate accumulation. In practice, many cases of chronic lactic acidosis are due to a combined imbalance between increased production and decreased metabolism

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, glucose, urea, Cr, AST, ALT, ALP, bilirubin, serum osmolality and osmolar gap, toxic alcohol levels, troponin, CK, INR, PTT
- **MICROBIOLOGY**—routine blood and urine C&S, consider culturing other bodily fluids as appropriate (e.g. CSF, pleural, pericardial, ascites)

INVESTIGATIONS (CONT'D)

- **IMAGING**—AXR ± CT abdomen (if suspect bowel ischemia)
- **ABG**

SPECIAL

- **INBORN ERROR OF METABOLISM** (mitochondrial disorder)—if suspected, consider LP for CSF lactate level ± muscle biopsy

MANAGEMENT

ACUTE—ABC, O_2 to keep S_pO_2 ≥92%, IV, HCO_3 bolus (1–2 amps), or infusion if extremely low pH (<7.2)

TREAT UNDERLYING CAUSE

Rhabdomyolysis

DIFFERENTIAL DIAGNOSIS

SKELETAL MUSCLE DAMAGE

- **MEDICATIONS**—alcohol, cocaine, statins, neuroleptic malignant syndrome, serotonin syndrome, malignant hyperthermia
- **HYPERACTIVITY**—seizures, exertion
- **IMMOBILITY**
- **COMPARTMENT SYNDROME**
- **TRAUMA OR SURGERY**
- **MYOPATHIES**—polymyositis, dermatomyositis

CARDIAC MUSCLE DAMAGE—myocardial infarction

PATHOPHYSIOLOGY

DEFINITION OF RHABDOMYOLYSIS—CK >5× of upper normal limit

HYPOCALCEMIA AND HYPERCALCEMIA—calcium initially decreases due to ↑ deposition in muscle and ↓ bone responsiveness to PTH. May see rebound hypercalcemia in 20% of patients when rhabdomyolysis resolves

COMPLICATIONS—acute kidney injury, DIC

INVESTIGATIONS

BASIC

- **LABS**—lytes, urea, Cr, CK, AST, ALT, Ca, PO_4, Mg, uric acid, troponin, LDH, urine myoglobin

DIAGNOSTIC ISSUES

MONITORING IN RHABDOMYOLYSIS—CK, urine output, Cr, Ca, PO_4 should be checked regularly (q4–24 h) until CK normalized

MANAGEMENT

ACUTE—**ABC**, O_2 to keep sat >90%, **IV**

PREVENT COMPLICATIONS—**NS** 3–4 L in first 3–4 h bolus, then 300 mL/h or more to prevent acute kidney injury. However, if acute kidney injury already established be careful not to cause fluid overload. Fasciotomy for compartment syndrome

Alkaline diuresis (add 3 amps $NaHCO_3$ to 1 L D5W to keep urine pH >6.5, little evidence for this)

SPECIFIC ENTITIES

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

- **PATHOPHYSIOLOGY**—an idiosyncratic reaction due to dopamine receptor blockade, usually with typical, and sometimes atypical, antipsychotic agents. The syndrome typically occurs within a few days of treatment, with drug levels usually within therapeutic range. May also develop after withdrawal of exogenous dopaminergic agonists, such as levodopa therapy in Parkinson's disease patients

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—**classic tetrad** of high fever, autonomic instability (tachycardia, hypertension), neuromuscular rigidity, and altered mental status. CK may be elevated if rigidity present
- **DIAGNOSIS**—clinical based on history and physical. Check CK
- **TREATMENTS**—discontinue all antidopaminergic medications. Supportive measures. Specific treatments include dantrolene, bromocriptine, and amantadine

SEROTONIN SYNDROME

- **PATHOPHYSIOLOGY**—overstimulation of central and peripheral serotonin receptors, usually related to overdose of SSRIs or drug interactions that increase serotonergic neurotransmission (e.g. SSRIs in combination with MAOIs or TCAs)

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—**classic triad** of autonomic instability (fever, tachycardia, hypertension), neuromuscular rigidity and altered mental status. CK may be elevated if rigidity present. While many of the symptoms may be similar to neuroleptic malignant syndrome, **shivering, hyperreflexia, myoclonus, and ataxia** may be present in serotonin syndrome but not in neuroleptic malignant syndrome
- **DIAGNOSIS**—clinical based on history and physical
- **TREATMENTS**—discontinue all serotonergic medications. Supportive measures. In mild cases, symptoms usually resolve within 24 h. Consider cyproheptadine in select cases

Toxicology

APPROACH TO OVERDOSE

HISTORY (brief)—collateral important, inquire about depression

PHYSICAL (brief)—pupils, lungs, heart, GI, skin

INVESTIGATIONS

- **BLOOD TESTS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, PTT, Ca, Mg, PO_4, β-hCG, alcohol level, methanol, ethylene glycol, salicylates, acetaminophen, other drug levels (especially patient's own medications such as digoxin, iron, theophylline, lithium), serum osmolality and osmolar gap
- **URINE TESTS**—urine pregnancy test (if female <50), urine drug screen (as appropriate and may not affect initial management; e.g. narcotics, benzodiazepines, cocaine, amphetamines, cannabinoids)
- **IMAGING**—CXR, CT head
- **ECG**
- **ABG**

URGENT MANAGEMENT—ABC, O_2, IV, monitor, vitals (HR, RR, BP, temp, O_2 sat, blood sugar, GCS)

ANTICHOLINERGIC SYNDROMES

CAUSES—TCAs, antihistamines, antipsychotics, anti-Parkinson medications, amantadine, antispasmodics, mydriatics, skeletal muscle relaxants

CLINICAL FEATURES—**common** (fever, tachycardia, hypertension, *dry/flushed skin*, delirium, hallucinations, mydriasis, urinary retention, decreased bowel sounds), **serious** (seizures, coma, respiratory failure, arrhythmias, cardiovascular collapse). ECG findings may include sinus tachycardia, prolonged PR, QRS, and QT intervals, RBBB and ST elevation in leads V1–V3

TREATMENTS—**supportive** measures, **charcoal**, **HCO_3** if cardiac arrhythmia, sedation with benzodiazepines PRN

ANTICHOLINERGIC SYNDROMES (CONT'D)

SYMPATHOMIMETIC SYNDROMES

CAUSES—cocaine, amphetamines/methamphetamines, LSD, PCP, phenylpropanolamine, ephedrine, pseudoephedrine, methylphenidate, nicotine, theophylline

CLINICAL FEATURES—**common** (fever, tachycardia, hypertension, *diaphoresis*, delusions, paranoia, mydriasis, hyperreflexia), **serious** (seizures, coma, arrhythmias, cardiovascular collapse)

TREATMENTS—**supportive** measures, **sedation** with benzodiazepines. Treat severe hypertension (nitroprusside, phentolamine). Avoid β-blockers (unopposed α effect). Control hyperthermia (cooling blanket, may require **paralysis** to limit muscular activity)

CHOLINERGIC SYNDROMES

CAUSES—organophosphate and carbamate insecticides, pilocarpine, physostigmine, edrophonium, some mushrooms

CLINICAL FEATURES—**common** (delirium, salivation, lacrimation, miosis, diaphoresis, emesis, urinary and fecal incontinence), **serious** (pulmonary edema, seizures, coma)

TREATMENTS—**supportive** measures, **atropine**

METHANOL AND ETHYLENE GLYCOL OVERDOSE

See METHANOL and ETHYLENE GLYCOL OVERDOSE on p. 117

ACETAMINOPHEN OVERDOSE

PATHOPHYSIOLOGY—5% of acetaminophen is metabolized to *N*-acetyl-p-benzoquinoneimine (NAPQI), which is highly toxic to liver, but is normally rapidly inactivated via conjugation with glutathione. With acetaminophen overdose, NAPQI accumulates due to depletion of glutathione stores, causing hepatic necrosis and acute kidney injury. *N*-acetylcysteine, the antidote, regenerates hepatic glutathione stores leading to enhanced conjugation and clearance of NAPQI. A single dose of 10–15 g acetaminophen (twenty 500 mg tablets) can produce liver injury. Fulminant hepatic failure (FHF) usually associated with >25 g

★The rule of 140's★ toxic dose = **140** mg/kg, Rumack-Matthew nomogram blood level vs. time (>**140** μg/mL 4 h after ingestion → >5 μg/mL 24 h after ingestion). First dose of N-acetylcysteine **140** mg/kg PO (IV infusion may also be used: 150 mg/kg in 200 mL D5W over 15 min, then 50 mg/kg in 500 mL D5W over 4 h, then 100 mg/kg in 1 L D5W over 16 h; may continue third stage until liver enzyme normalization in FHF)

CLINICAL FEATURES—first few hours, nausea and vomiting, RUQ pain, diarrhea. Symptoms disappear 24 h after ingestion. Liver failure (↑ INR, bilirubin, and transaminases) may start at 24–72 h with or without AKI or cardiotoxicity

POOR PROGNOSTIC SIGNS—coagulopathy (most important), acidosis, acute kidney injury, hypophosphatemia, encephalopathy

TREATMENTS—supportive, ***N*-acetylcysteine** (duration of therapy controversial; if evidence of hepatic injury, continue NAC until transaminases decreasing, INR ≤2, and serum acetaminophen concentration undetectable)

KING'S COLLEGE CRITERIA FOR LIVER TRANSPLANTATION IN TYLENOL OVERDOSE

★THE RULE OF 3'S★—either pH <7.**3** or grade **III**/IV encephalopathy plus Cr >**3**00 μmol/L [>**3.3** mg/dL] plus INR >**6.5** (or PT >100 s) (~5% survival with medical therapy alone)

NEJM 2008 359:3

SALICYLATE OVERDOSE

CAUSES (★The rule of 3's★)—a single dose of 10–**3**0 g (**3**0 tablets of **3**25 mg) can be fatal. Symptoms may occur with salicylate >**3.0** mmol/L [>40 mg/mL]

SALICYLATE OVERDOSE (CONT'D)

CLINICAL FEATURES—**common** (tinnitus, vertigo, N&V, diarrhea, tachypnea, metabolic acidosis, respiratory alkalosis), **serious** (hyperthermia, pulmonary edema, delirium, seizure, coma)

DIAGNOSIS—salicylate level (every 2 h until decreased level), ABG (every 2 h until stable)

TREATMENTS—**supportive** measures (avoid intubation if possible). Consider gastric lavage. ***Glucose*** 100 mL of D50W IV if altered mental status regardless of serum glucose level. **Activated charcoal** (50–100 g PO/NG q4h × 3doses). **Alkalinize** serum and urine; maintain urine pH 8–8.5 (***NaHCO*$_3$** 1–3 amps IV push, then 3 amps of $NaHCO_3$ in 1 L D5W at 250 mL/h). Consider **hemodialysis** if altered mentation, cerebral edema, fluid overload, pulmonary edema, severe renal failure, salicylate >7.2 mmol/L [>100 mg/mL] in acute ingestion or >5 mmol/L [>70 mg/mL] in chronic toxicity, rising levels or clinical deterioration

MORTALITY RATE—acute ~1–2% (usually suicidal attempt in young patient), chronic ~25% (often elderly patient, delayed diagnosis due to low index of suspicion)

OPIATE, SEDATIVE OR ETHANOL INTOXICATION SYNDROMES

CAUSES—narcotics, barbiturates, benzodiazepines, ethanol, clonidine

CLINICAL FEATURES—**common** (decrease in all vitals, hypothermia, stupor, miosis, dry skin, urinary retention, decreased bowel sounds, hyporeflexia), **serious** (seizures, coma, respiratory depression). Note vitals may be relatively normal, particularly for benzodiazepine overdose

TREATMENTS—**supportive** measures, **naloxone** (if opiates), **flumazenil** (if benzodiazepines), **urinary alkalinization** (if barbiturates)

β-BLOCKER OVERDOSE

CLINICAL FEATURES—**common** (hypotension, bradycardia, bronchospasm, hypoglycemia), **serious** (shock, asystole, seizure, coma)

TREATMENTS—**supportive** measures, **fluid** resuscitation, **glucagon** (initial dose 0.05–0.15 mg/kg up to a max dose of 10 mg over 2 min, then infusion 0.07 mg/kg), **IV calcium, phosphodiesterase inhibitor** (milrinone or amrinone), **epinephrine, dialysis** (for atenolol, sotalol, acebutolol or nadolol), high dose **insulin/glucose infusions, intravenous lipid emulsion therapy. Atropine or pacing** not usually effective. Consider intra-aortic balloon pump (IABP) or extracorporeal membrane oxygenation (ECMO) in severely poisoned

CALCIUM CHANNEL BLOCKERS OVERDOSE

CAUSES—dihydropyridine calcium channel blockers (nifedipine, amlodipine, isradipine) affect mainly vascular tone and may cause hypotension with reflex tachycardia. Non-dihydropyridine calcium channel blockers (diltiazem, verapamil) usually lead to SA/AV slowing and negative inotropy

CLINICAL FEATURES—**common** (hypotension, arrhythmias, delirium, hypokalemia, lactic acidosis, hyperglycemia)

TREATMENTS—**supportive** measures. **Fluid** resuscitation, catecholamines, **IV calcium** (*calcium gluconate* 10% 50 mL or *calcium chloride* 10% 20 mL)**, glucagon, high dose insulin/glucose infusions, intravenous lipid emulsion therapy. Hemodialysis not effective.** Consider IABP or ECMO in severely poisoned

LITHIUM TOXICITY

CAUSES—usually related to chronic drug accumulation, although acute overdose may occur. Commonly precipitated by renal failure and dehydration. Therapeutic Li levels 0.6–1.2 mEq/L, mild toxicity = 1.5 to <2.5 mEq/L, moderate toxicity = 2.5–3.5 mEq/L, severe toxicity >3.5 mEq/L

CLINICAL FEATURES—**acute toxicities** include CNS (confusion, ataxia, seizures, coma), neuromuscular (tremors, fasciculations, rigidity, weakness), and others (sinus bradycardia, hypotension, ARDS, acute renal failure, nausea and vomiting, diarrhea, leukocytosis, hypercalcemia). **Chronic toxicities** include nephrogenic diabetes insipidus, leukocytosis, and goiter

TREATMENTS—**supportive** measures, gastric lavage if within 60 min of ingestion, fluid resuscitation with NS followed by **hypotonic solution** infusion if nephrogenic diabetes insipidus, Kayexalate (binds lithium), whole bowel irrigation, **hemodialysis** (if Li >3.5 mEq/L in acute ingestion or >2.5 mEq/L in chronic ingestion AND significant symptoms, or persistently high Li levels, beware of rebound effect after hemodialysis due to redistribution)

Related Topics
ABG (p. 88)
Alcohol Abuse (p. 117)
Delirium/Coma (p. 432)
ECG (p. 73)
Seizures (p. 350)

DIAGNOSTIC ISSUES FOR OVERDOSE

OSMOLAR GAP—measured osmolality – calculated osmolality

- **$Osmo_{calc}$** = (**G**lucose in mmol/L) + (**U**rea in mmol/L) + 2 × (**Na** mmol/L) ★**GUN2**★
- US units: **$Osmo_{calc}$** = (**G**lucose in mg/dL)/18 + (**U**rea in mg/dL)/2.8 + 2 × (**Na** mEq/L)
- **NORMAL OSMOLAR GAP**—typically 2 to +6 mOsm/kg
- **INCREASED OSMOLAR GAP AND ANION GAP**—ethylene glycol, methanol, diabetic or alcoholic ketoacidosis, lactic acidosis, chronic renal failure (other small solutes), severe lactic acidosis ("idiogenic osmole"), severe sepsis (some inflammatory mediators are believed to be osmotically active)
- **INCREASED OSMOLAR GAP BUT NORMAL ANION GAP**— ethanol, isopropyl alcohol, diethyl ether, sorbitol, mannitol, severe hyperproteinemia, severe hyperlipidemia

ANION GAP (AG)—$Na - Cl - HCO_3$. AG >12 mEq/L is abnormal and can be caused by methanol, ethylene glycol, uremia, ketoacidosis, paraldehyde, INH, iron, lactic acidosis, cyanide, arsenic, toluene, salicylates (see METABOLIC ACIDOSIS p. 87). Decreased anion gap can be caused by excessive cations such as in Li toxicity. Remember to adjust AG in hypoalbuminemia by adding 2.5–3 mmol/L for every 10 g/L [1.0 g/dL] decrease in serum albumin. A "normal" AG may actually be elevated in the setting of hypoalbuminemia

OXYGEN SATURATION GAP—>5% difference between pulse oximetry and oxygen saturation on ABG is seen with carbon monoxide, cyanide, hydrogen sulfide, and methemoglobin poisoning

ANTICHOLINERGIC AND SYMPATHOMIMETIC SYNDROMES—anticholinergic syndromes lead to dry skin whereas sympathomimetic syndromes are associated with diaphoresis

MANAGEMENT OF OVERDOSES

1. **ACUTE**—ABC, **O_2**, IV, **universal antidote** (*glucose* 25–50 g IV if capillary glucose measurement not immediately available, *naloxone* 0.4–2 mg IV, *thiamine* 50–100 mg IV). Supportive care for airway protection (intubation if GCS ≤8, severe hypoxemia/hypercapnia and/or hemodynamic instability), blood pressure (fluids, vasoactive drugs), arrhythmias, agitation, and seizures
2. **DECONTAMINATION**—***activated charcoal*** 50–100 g PO with 60 mL sorbitol (within 1 h ingestion of most drugs except those that are rapidly absorbed). Avoid if bowel obstruction,

MANAGEMENT OF OVERDOSES (CONT'D)

perforation, or endoscopy is contemplated. **Gastric lavage** with 2–3 mL/kg aliquots if within 60 min of ingestion (should be tried even after 60 min if delayed gastric emptying, e.g. TCA overdose) and if charcoal not indicated (e.g. iron, lithium, cyanide). **Whole bowel irrigation** (*Polyethylene glycol* 2 L/h, up to 10 L). **Skin** (remove clothing, cleanse). Ipecac not recommended

3. **ALKALINIZATION AND/OR HEMOPERFUSION/HEMODIALYSIS**—**forced alkaline diuresis** will accelerate excretion of acids (aspirin, barbiturates). Give 3 amps of $NaHCO_3$ in 1 L D5W at 250 mL/h. Monitor urine output and for volume overload, alkalosis and hypokalemia. Goal pH for urine is 7.5–8 and for serum is 7.5–7.6. Consider **hemodialysis** if the patient is toxic with barbiturate, bromides, chloral hydrate, alcohols (ethanol, isopropanol, acetone, methanol, ethylene glycol), lithium, procainamide, theophylline, salicylates, heavy metals, trichloroethanol, atenolol, sotalol, acebutolol or nadolol
4. **SPECIFIC ANTIDOTES**—**acetaminophen** (*N-acetylcysteine* 150 mg/kg (~60 mL) in 200 mL D5W IV over 1 h, then 50 mg/kg (~20 mL) in 500 mL D5W IV over 4 h, then 100 mg/kg (~40 mL) in 1 L D5W IV over 16 h. Alternatively, *N-acetylcysteine* 140 mg/kg PO/NG, followed by 70 mg/kg q4h for 17 doses).

MANAGEMENT OF OVERDOSES (CONT'D)

Opiates (*naloxone* 0.4–2 mg IV, repeat PRN). **Benzodiazepines** (*flumazenil* 0.2 mg over 30 s, then 0.5 mg q1min PRN. Maximum total dose 3 mg). **Methanol/ethylene glycol** (*10% ethanol* in D5W 10 mL/kg IV over 30 min, then 1.5 mL/kg/h, goal EtOH level 22–28 mmol/L [100–128 mg/dL]. *Fomepizole* 15 mg/kg IV, followed by 10 mg/kg q12h until ethylene glychol level <3.2 mmol/L [<20 mg/dL]). **Digitalis** (*Digibind* 10–20 vials IV if life-threatening arrhythmia). **Calcium channel blockers** ($CaCl_2$ 1 g over 5 min, repeat if life-threatening disease). **β-blockers** (*glucagon* initial dose 0.05–0.15 mg/kg up to a max dose of 10 mg over 2 min, then infusion 0.07 mg/kg). **Isoniazid** (*pyridoxine* given gram-to-gram of INH ingested). **Tricyclic antidepressant** ($NaHCO_3$ 1–2 mmol/kg IV if cardiac arrhythmia). **Anticholinergics** (*lorazepam* 2–10 mg IV q5min, physostigmine). **Iron** (*deferoxamine* 1 g IM or IV, then 500 mg q4h × 2, then 500 mg q4–12 h PRN. Maximum total dose 6 g/day). **Cholinergics** (*atropine* 0.5–2 mg IV, repeat q5–30 min PRN)

5. **ANTICIPATE COMPLICATIONS**—delirium, aspiration pneumonia, respiratory failure, electrolyte imbalances, arrhythmias, hypotension, seizures, and others. Consider ICU/CCU consultation where appropriate
6. **PSYCHIATRY CONSULT WHEN STABLE**

Alcohol Withdrawal and Complications of Alcoholism

PATHOPHYSIOLOGY

ALCOHOLIC EQUIVALENTS—360 mL (12 oz) of beer = 150 mL (5 oz) of wine = 45 mL (1.5 oz) of distilled spirits = 12 g of alcohol (a standard drink)

AT RISK FOR ALCOHOLISM— > 14 drinks/week or >4 drinks/session for men and >7 drinks/week or >3 drinks/session for women. Alcoholic cirrhosis requires >80 g/day (8 beers, 1 bottle of wine, or 250 mL of hard liquor) for 10–20 years

COMPLICATIONS OF ALCOHOLISM

- **ACUTE INTOXICATION**
- **ACUTE WITHDRAWAL**—minor withdrawal, seizures, hallucinations, delirium tremens
- **CHRONIC ALCOHOLISM**
  - **NEUROLOGIC**—Wernicke–Korsakoff syndrome, cognitive dysfunction, cerebellar degeneration, Marchiafava–Bignami disease, peripheral neuropathy, myopathy
  - **PSYCHIATRIC**—dependence, depression, homicide, suicide

PATHOPHYSIOLOGY (CONT'D)

- **CARDIOVASCULAR**—hypertension, coronary heart disease, dilated cardiomyopathy, arrhythmias
- **LIVER**—fatty liver, alcoholic hepatitis, cirrhosis
- **PANCREAS**—acute or chronic pancreatitis
- **NUTRITION**—hypokalemia, hypomagnesemia, hypophosphatemia, malnutrition, overweight
- **HEMATOLOGY**—macrocytic anemia, thrombocytopenia, splenomegaly
- **CANCER**—oral cavity, esophagus, pharynx, larynx, liver, breast
- **ENDOCRINE**—alcoholic hypoglycemia and ketosis, pseudo-Cushing's, hyperuricemia, hypogonadism
- **SOCIAL**—accidents, domestic violence, fetal alcohol syndrome

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE AN ALCOHOL PROBLEM?

CAGE—**C**ut down, **A**nnoyed by criticisms, **G**uilty about drinking, **E**ye-opener. *Sens 0.49–0.69, Spc 0.75–0.95, LR+ of CAGE ≥2 for adult alcohol abuse or dependence 6.9, LR- 0.33*

OTHERS—MAST, AUDIT

APPROACH—"use CAGE for screening heavy drinking (>8 drinks/day). Score of 0 has good NPV at low prevalence of disease. Scores of 3 or 4 strongly support diagnosis of alcohol abuse. Scores of 1 or 2 must be interpreted with caution. Note that CAGE is relatively insensitive in detecting hazardous drinking but lower amounts or drinking in pregnancy"

JAMA 1994 272:22

The Rational Clinical Examination. McGraw-Hill, 2009

DSM IV CRITERIA FOR ALCOHOL WITHDRAWAL

A. Cessation/reduction of alcohol use that has been heavy and prolonged
B. Two or more of the following within several hours to a few days of cessation: autonomic hyperactivity (e.g. sweating, tachycardia), tremor, insomnia, nausea or vomiting, transient visual, tactile, or auditory hallucinations or illusions, psychomotor agitation, anxiety, grand mal seizures
C. Symptoms causing clinically significant distress or impairment in social or occupational function
D. Rule out general medical conditions or other mental disorders

MINOR WITHDRAWAL

- **TIMING**—occurs within 6 h of cessation, resolves in 24–48 h
- **SYMPTOMS**—due to CNS and sympathetic hyperactivity, may include insomnia, tremulousness, mild anxiety, gastrointestinal upset, headache, diaphoresis, palpitations, anorexia

ALCOHOLIC HALLUCINATIONS

- **TIMING**—develop within 12–24 h of abstinence and resolve within 24–48 h
- **SYMPTOMS**—usually visual, although auditory and tactile phenomena may also occur. Unlike DT, there is usually no decreased level of consciousness/global confusion

WITHDRAWAL SEIZURES

- **TIMING**—usually occur within 48 h after the last drink; however, may occur after only 2 h of abstinence

CLINICAL FEATURES (CONT'D)

- **SYMPTOMS**—generalized tonic–clonic convulsions. Predominantly seen in patients with a long history of chronic alcoholism. Be wary of intracerebral hemorrhage with focal seizures

DELIRIUM TREMENS (DT)

- **TIMING**—typically begin between 48 and 96 h after the last drink and lasts 1–5 days
- **SYMPTOMS**—hallucinations, disorientation, tachycardia, hypertension, low-grade fever, agitation, and diaphoresis
- **RISK FACTORS**—age >30, history of sustained drinking, history of previous delirium tremens, concurrent illness, greater number of days since the last drink

INVESTIGATIONS

BASIC

- **LABS**—CBCD (macrocytosis, cytopenias), lytes, urea, Cr, glucose, TSH, AST, ALT (AST/ALT >2), ALP, bilirubin, GGT, Ca, Mg, PO_4, osmolality
- **MICROBIOLOGY**—blood C&S, urinalysis, urine C&S (if delirious)
- **IMAGING**—CXR
- **ECG**
- **ABG**
- **URINE DRUG SCREEN**

SPECIAL

- **CARBOHYDRATE DEFICIENT TRANSFERRIN**—sens 60–70%, spc 80–90%
- **HEAD CT**—if significant or prolonged delirium, focal neurologic deficits, or focal seizures

ACUTE MANAGEMENT OF ALCOHOL WITHDRAWAL

ACUTE—**ABC**, O_2 to keep S_pO_2 ≥92%, **IV** (1 L crystalloid bolus, then 100 mL/h). Consider causes of patient's symptoms other than alcohol withdrawal

TREAT/PREVENT COMPLICATIONS

- **SEIZURES OR DELIRIUM TREMENS**—*diazepam* 5–10 mg IV q5min OR *lorazepam* 1–2 mg IV q5min until patient calm, then put on high-risk protocol
- **HIGH RISK FOR WITHDRAWAL** (fixed schedule dosing)—*chlordiazepoxide* 50–100 mg PO q6h and PRN×1 day, then 25–50 mg q6h and PRN×2 days. Alternatively, consider CIWA-Ar scale below
- **LOW RISK FOR WITHDRAWAL** (as needed dosing)—*diazepam* 10–20 mg PO q2h or *lorazepam* 1–2 mg PO q1h until no symptoms then PRN doses

ACUTE MANAGEMENT OF ALCOHOL WITHDRAWAL (CONT'D)

- **AGITATION**—add *haloperidol* 0.5–5 mg PO/IM/IV q1–4 h PRN (but may lower seizure threshold)
- **TREMORS**—**β-blockers**
- **REFRACTORY DELIRIUM TREMENS**—*propofol, phenobarbital or dexmedetomidine*

NUTRITIONAL SUPPLEMENT—**thiamine deficiency** (*thiamine* 100 mg IV/IM × 5 days must be given before any glucose solution, or may worsen Wernicke encephalopathy); consider high dose thiamine for Wernicke encephalopathy (500 mg IV TID × 2 days, 500 mg IV/IM daily × 5 days). ***Multivitamin*** 1 tab PO daily. Replace electrolytes (K, Mg, PO_4) if low

LONG-TERM MANAGEMENT OF ALCOHOLISM

COUNSELING—**support social network** (Alcoholics Anonymous, counseling). **Abstinence programs** (outpatient, inpatient). **Education** (alcoholism is a chronic-relapsing disease, explain withdrawal)

MEDICATIONS—***naltrexone*** 25 mg PO daily × 1 week, then 50 mg PO daily for at least 3–4 months, coupled with psychosocial intervention may be used for alcohol dependence. Depot injection can be used if significant risk of nonadherence. A derivative of naltrexone, nalmefene, is available in Europe. **Disulfiram**, which causes a highly unpleasant sensation when patient consumes alcohol, is another option. ***Acamprosate*** 333–666 mg PO q8h can be used in patients with liver disease

TREATMENT ISSUES FOR ALCOHOL WITHDRAWAL

REVISED CLINICAL INSTITUTE WITHDRAWAL ASSESSMENT FOR ALCOHOL (CIWA-A R) SCALE (for use in patients who are able to answer questions)

- **NAUSEA AND VOMITING** (0–7)—"Do you feel sick to your stomach? Have you vomited?"
- **TREMOR** (0–7)
- **PAROXYSMAL SWEATS** (0–7)
- **ANXIETY** (0–7)—"Do you feel nervous?"
- **AGITATION** (0–7)
- **TACTILE DISTURBANCES** (0–7)—"Do you have any itching, pins-and-needles sensations, burning, or numbness, or do you feel like bugs are crawling on or under your skin?"
- **AUDITORY DISTURBANCES** (0–7)—"Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?"

TREATMENT ISSUES FOR ALCOHOL WITHDRAWAL (CONT'D)

- **VISUAL DISTURBANCES** (0–7)—"Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?"
- **HEADACHE, FULLNESS IN HEAD** (0–7)—"Does your head feel different? Does it feel like there is a band around your head?"
- **ORIENTATION AND CLOUDING OF SENSORIUM** (0–4)—"What day is this? Where are you? Who am I?"
- **UTILITY**—mild withdrawal ≤8/67 points, moderate withdrawal 9–15 points, severe withdrawal >15 points (higher risk of delirium tremens and seizures). Use of benzodiazepines recommended when score ≥9. Symptom-triggered regimens require intense monitoring, but have been shown to result in less medication use and shorter duration of treatment

SPECIFIC ENTITIES

THIAMINE DEFICIENCY SYNDROMES

- **WERNICKE'S ENCEPHALOPATHY**—encephalopathy (profound disorientation, indifference, inattentiveness, delirium, altered level of consciousness), oculomotor dysfunction (nystagmus, lateral rectus palsy, and conjugate gaze palsies), gait ataxia
- **KORSAKOFF'S AMNESIA** (irreversible)—selective anterograde and retrograde amnesia, confabulation, apathy, intact sensorium, relative preservation of long-term memory and other cognitive skills

METHANOL AND ETHYLENE GLYCOL OVERDOSE

- **CAUSES**—methanol and ethylene glycol can be found in anti-freeze, de-icing solutions, windshield fluids, cleaners, solvents, and fuels. The methanol metabolite formate and the ethylene glycol metabolites glycolate, glyoxylate, and oxalate result in toxic injuries. A lethal dose is around 1 g/kg
- **CLINICAL FEATURES**—anion (and osmolar) gap metabolic acidosis with associated Kussmaul breathing, hypotension, seizures, and altered level of consciousness. Methanol specifically is associated with mydriasis, afferent pupillary defect, optic disc hyperemia, retinal edema resulting in permanent blindness and ischemic injury to the basal ganglia. Ethylene glycol can result in cranial nerve palsies, tetany, and acute kidney injury due to crystalline nephropathy

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—**supportive** measures. **NG suction** may be helpful if recent ingestion (but not activated charcoal). ***NaHCO$_3$*** 1–2 amps IV bolus, then 3 amps in 1 L D5W at 250 mL/h (if metabolic acidosis pH <7.3. Helps to minimize tissue penetration and damage). **Alcohol dehydrogenase inhibition** (*fomepizole* 15 mg/kg IV, followed by 10 mg/kg q12h) or **continuous ethanol infusion** (IV 8 mL/kg 10% ethanol in D5W over 30 min then 1.5–2 mL/kg/h to maintain serum ethanol >21 mmol/L, increase rate to 3 mL/kg/h on dialysis; alternatively PO 1 mL/kg 95% ethanol then 0.15 mL/kg/h ≈ 4 oz Scotch loading dose with 2 oz q1h maintenance). **Cofactor therapy** includes *folic acid* 50 mg IV q4h until methanol no longer measurable (accelerates formic acid → $CO_2 + H_2O$); *thiamine* 100 mg IV q6h and *pyridoxine* 50 mg IV q6h until ethylene glycol no longer measurable (accelerates glycoxylate → glycine + α-hydroxy-β-ketoadipate. This reaction requires magnesium supplementation). **Hemodialysis** for confirmed intoxication (methanol level >15.6 mmol/L [>500 µg/mL] or ethylene glycol level >8 mmol/L [>50 mg/dL]), refractory metabolic acidosis, or acute kidney injury. Folic acid, thiamine, and multi-vitamin as supportive measures

Hypothermia

CAUSES

INCREASED HEAT LOSS

- **ENVIRONMENTAL**—cold exposure
- **DERMATOLOGIC**—burns, extensive psoriasis, vasodilation (drugs, alcohol, sepsis, pancreatitis)
- **IATROGENIC**—cold fluid infusion, CPR, renal replacement therapy

DECREASED METABOLISM

- **ENDOCRINE**—hypothyroidism, hypopituitarism, adrenal insufficiency, hypoglycemia
- **METABOLIC**—anorexia nervosa, malnutrition

ALTERED REGULATION

- **CENTRAL**—stroke, Parkinson's disease, multiple sclerosis, hypothalamic dysfunction, anorexia nervosa, drugs (barbiturate, TCA, sedatives, alcohol)
- **PERIPHERAL**—neuropathies, diabetes

PATHOPHYSIOLOGY

DEFINITION OF HYPOTHERMIA—internal temperature <35 °C [<95 °F] (by rectal, tympanic, or esophageal thermometer). Hypothermia may be mild (34–35 °C [93–95 °F]), moderate (30–34 °C [86–93 °F]), or severe (<30 °C [<86 °F])

RISK FACTORS—extremes of age, alcoholism, malnutrition, homelessness, mental illness

COMPLICATIONS—hypothermia affects most organs, causing cognitive (coma), neuromuscular (rigidity), respiratory (pulmonary edema), cardiac (arrhythmia), and cutaneous (frostbite) complications. Sepsis, pneumonia, hypokalemia, hypoglycemia, and rhabdomyolysis may also occur

CLINICAL FEATURES

HISTORY—exposure to cold (duration, environment), shivering, confusion, delirium, palpitations, weakness, ulcers, frostbite, fever, weight loss, past medical history (hypothyroidism, diabetes, alcoholism, psoriasis), medications, social history

PHYSICAL—vitals (bradycardia, apnea, hypertension/hypotension, hypoxemia), GCS, respiratory and cardiovascular examination (arrhythmia), rigidity, hyporeflexia, skin examination (frostbite, burns, psoriasis)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, CK, troponin, AST, ALT, ALP, bilirubin, TSH, urinalysis, random cortisol
- **MICROBIOLOGY**—blood cultures
- **ECG**—Osborn wave (elevated J point), prolonged RR, PR, QRS, and QT intervals

MANAGEMENT

ACUTE—**ABC**, O_2 to keep sat >94%, **IV, rewarming**. Caution with fluid overload (decreased cardiac output in hypothermic patients) and vasopressors (arrhythmogenic potential). Resuscitation should continue until patient completely rewarmed

MONITORING—continuous cardiac monitoring. Also closely monitor electrolytes and glucose. Vagotonic maneuvers (e.g. intubation or suctioning) may precipitate asystole

REWARMING—**environment** (remove cold clothing. Warming blanket). **Active rewarming** (warm IV

MANAGEMENT (CONT'D)

fluids ~40–42 °C [104–108 °F]. If severe hypothermia, consider colonic/bladder irrigation, peritoneal or pleural lavage, extracorporeal blood rewarming. Goal of rewarming is 0.5–2 °C/h [1.8 °F/h] to minimize risk of VF and hypovolemic shock)

FROSTBITE—supportive care. Skin grafting and amputation may be required if gangrene develops

SPECIFIC ENTITIES

ELECTRICAL INJURY

- **PATHOPHYSIOLOGY**—causes include lightening, taser, and stun gun
- **CLINICAL FEATURES**—injuries may involve the skin (burns), heart (VF, asystole, cardiac contusion), bones/muscles (deep electrothermal tissue injury, osteonecrosis, compartment syndrome, rhabdomyolysis with renal failure, posterior shoulder dislocation), and neurologic system (loss of consciousness, weakness or paralysis, respiratory depression, autonomic dysfunction)

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—clinical. Obtain CBCD, lytes, urea, Cr, glucose, CK, appropriate imaging, drug and alcohol levels, urinalysis, CXR, ABG, ECG
- **TREATMENTS**—ABC, O_2, IV. Supportive management of complications. Monitor for compartment syndromes. Psychiatry consult for post-traumatic stress disorder

SUBMERSION INJURY (drowning)

- **CLINICAL FEATURES**—assess for cause of drowning (accidental, suicidal, alcohol or illicit drug use, concomitant myocardial infarction/stroke). Complications include respiratory failure, ARDS, hypothermia, arrhythmia (atrial fibrillation, bradycardia, ventricular tachycardia), acidosis (metabolic, respiratory), anoxic brain injury, cerebral edema, and seizures
- **DIAGNOSIS**—clinical. Obtain CBCD, lytes, urea, Cr, glucose, osmolality, drug and alcohol levels, urinalysis, CXR, ABG, and ECG
- **TREATMENTS**—ABC, O_2, IV. Supportive management of complications. 75% of near-drowning victims survive

Smoke Inhalation

PATHOPHYSIOLOGY

MECHANISM OF INJURY—thermal injury, hypoxic gas inhalation, bronchopulmonary toxins (airway inflammation and possible ARDS), and systemic toxins (CO, CN)

CLINICAL FEATURES

HISTORY—exposure to smoke (duration, substance, environment, deaths at the scene), dyspnea, chest pain, confusion, loss of consciousness, burns, other injuries, past medical history (respiratory disorders), medications

PHYSICAL—vitals (tachycardia, tachypnea, hypotension, temperature, hypoxemia), GCS, respiratory examination (cyanosis, cherry red lips, accessory muscle use, wheeze), cardiovascular examination (HF), burns, screening abdominal and neurologic examination

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, carboxyhemoglobin level, cyanide level, methemoglobin level (↓ with cyanide poisoning), lactate (↑ with cyanide poisoning)
- **IMAGING**—CXR

INVESTIGATIONS (CONT'D)

- **ECG**
- **ABG**—to determine PaO_2, $PaCO_2$, and CO-Hb levels
- **LARYNGOSCOPY/BRONCHOSCOPY**—if significant burns

MANAGEMENT

ACUTE—**ABC**, high flow O_2 to keep S_pO_2 ≥92% (100% FiO_2 if CO poisoning suspected pending ABG; see below), **IV**. Consider early **intubation** if severe injury/symptoms. Salbutamol and ipratropium

SPECIFIC POISONING—see CO and CN poisoning

BURNS—fluids, wound care. Plastic surgery consult

SPECIFIC ENTITIES

CARBON MONOXIDE (CO) POISONING

- **PATHOPHYSIOLOGY**—CO is an odorless, colorless, and non-irritating gas. It has a high affinity for hemoglobin, preventing it from releasing O_2
- **CLINICAL FEATURES**—nausea, malaise, headache, dyspnea, angina, confusion, coma
- **TREATMENTS**—100% FiO_2 (decreases $t_{½}$ of CO from 4 to 1.5 h). Hyperbaric oxygen may be

SPECIFIC ENTITIES (CONT'D)

used in selected patients (CO >25%, end-organ ischemia, or loss of consciousness); however, logistically challenging in critically ill patient

CYANIDE (CN) POISONING

- **PATHOPHYSIOLOGY**—produced by combustion of common household materials (polyurethane, nylon, wool, and cotton). CN binds to iron-containing enzymes (e.g. cytochrome) inhibiting aerobic metabolism
- **CLINICAL FEATURES**—severe lactic acidosis, cardiac dysfunction, apnea, coma
- **TREATMENTS**—cyanide antidote kit (inhaled amyl nitrite, intravenous sodium nitrite, sodium thiosulfate)

Anaphylaxis

See ANAPHYLAXIS (p. 423)

5
GASTROENTEROLOGY

Angeli Chopra

Nausea and Vomiting

DIFFERENTIAL DIAGNOSIS

NEUROLOGIC

- **ORGANIC**—infections, tumors, multiple sclerosis, vestibular nerve or brain stem lesions
- **DRUGS**—chemotherapy, SSRI, opioids, antibiotics, hormonal therapy, chronic marijuana use
- **PSYCHIATRIC**—anorexia nervosa, bulimia nervosa, rumination

GASTROINTESTINAL

- **INFECTIONS**—acute gastroenteritis, food poisoning, UTI, pyelonephritis, pneumonia
- **NEOPLASTIC**—gastric, ovarian, paraneoplastic, renal
- **OBSTRUCTION**—stomach, small bowel, colon, functional, gastric volvulus
- **POSTOP**—vagotomy, gastrectomy, fundoplication
- **INFLAMMATION**—esophagus, stomach, duodenum
- **GASTROPARESIS**—ischemic, diabetic, amyloidosis, scleroderma, drugs
- **OTHERS**—eosinophilic gastroenteritis, hepatobiliary disease, pancreatic disease, peritoneal irritation, functional gastrointestinal disorders, retroperitoneal fibrosis

METABOLIC

- **ENDOCRINE**—diabetes, adrenal insufficiency, hypercalcemia, hyperthyroidism, hyperparathyroidism, hyperemesis gravidarum, porphyria
- **OTHERS**—uremia, pregnancy, migraine

IDIOPATHIC

PATHOPHYSIOLOGY

REFLEX PATHWAY

- **AFFERENT**—(1) **humoral factors** (drugs, toxins, neurotransmitter, peptides) → area postrema in floor of 4th ventricle (chemoreceptor trigger zone) → **nucleus tractus solitarius** (NTS) in medulla serves as central pattern generator for vomiting; (2) neuronal **GI tract** stimuli → vagus nerve → NTS; (3) **nociceptive** stimuli → sympathetic nervous system → brain stem nuclei and the hypothalamus
- **EFFERENT**—NTS → **paraventricular nuclei** of the hypothalamus and the limbic and cortical regions → gastric electromechanical events are perceived as normal sensations or nausea or discomfort → vagus nerve → gastric and lower esophageal sphincter relaxation, retrograde contraction in proximal small bowel and antrum, abdominal muscle contraction and initial cricopharyngeus contraction followed by relaxation seconds before vomiting

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, Ca, Mg, PO_4, AM cortisol, urinalysis
- **MICROBIOLOGY**—urine C&S
- **IMAGING**—CXR, AXR

SPECIAL

- **GASTROSCOPY, GASTRIC EMPTYING STUDY**
- **CT HEAD**

MANAGEMENT

SYMPTOM CONTROL

- **H1 ANTAGONISTS**—*dimenhydrinate* 25–50 mg PO/PR q4h, *diphenhydramine* 25–50 mg PO/IV/IM q4h, *cyclizine* 50 mg PO/IM q4h or 100 mg PR q4h, *meclizine* 25–50 mg PO daily, *promethazine* 12.5–25 mg PO/IM q4h or 12.5–25 mg PR daily
- **D2 ANTAGONISTS**—**benzamides** (*metoclopramide* 5–10 mg PO/IV/IM q4h), **phenothiazine** (*prochlorperazine* 5–10 mg PO q6–8 h, *chlorpromazine* 10–25 mg PO q4–6 h),

D. Hui et al. (eds.), *Approach to Internal Medicine: A Resource Book for Clinical Practice*,
DOI 10.1007/978-3-319-11821-5_5, © Springer International Publishing Switzerland 2016

MANAGEMENT (CONT'D)

butyrophenones (*droperidol* 1.25–5 mg IM q4h, *haloperidol* 0.5–1 mg IV/PO q4h)
- **5HT3 ANTAGONISTS**—*ondansetron* 4–8 mg PO/IV q8h, *granisetron* 2 mg PO or 1 mg IV, *dolasetron* 100 mg PO/IV daily
- **M1 ANTAGONISTS**—*scopolamine* 1.5 mg TD q72h
- **STEROID**—*dexamethasone* 4 mg PO/SC/IV BID–TID
- **TUBE FEED**—NJ tube, G tube

TREAT UNDERLYING CAUSE

Related Topics
Chemotherapy-Induced Nausea and Vomiting (p. 254)
Nausea and Vomiting in the Palliative Setting (p. 448)

Dysphagia

DIFFERENTIAL DIAGNOSIS

OROPHARYNGEAL (upper esophagus and pharynx, or upper esophageal sphincter dysfunction)
- **NEUROLOGICAL**—stroke, multiple sclerosis, Parkinson's, dementia, amyotrophic lateral sclerosis, Guillain–Barre, myasthenia gravis, cerebral palsy, Huntington's, tardive dyskinesia, brain stem tumors, trauma
- **MYOPATHIC**—myotonic dystrophy, dermatomyositis, connective tissue disease, sarcoidosis, paraneoplastic
- **STRUCTURAL**—cricopharyngeal bar, Zenker's diverticulum, cervical webs, oropharyngeal tumors, osteophytes and skeletal abnormality, congenital abnormality, ill-fitting dentures
- **INFECTIOUS**—syphilis, Lyme disease, botulism, mucositis
- **METABOLIC**—Cushing's, thyrotoxicosis, Wilson's, amyloidosis, Sjögren's syndrome
- **IATROGENIC**—chemotherapy, neuroleptics, postsurgical, radiation
- **FUNCTIONAL (GLOBUS SENSATION)**

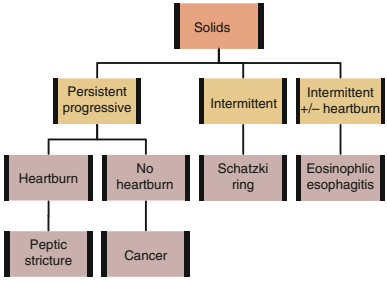
ESOPHAGEAL (body of esophagus, lower esophageal sphincter, cardia)
- **STRUCTURAL**—**tumors** (benign, malignant), **esophagitis/stricture** (reflux, caustic/erosive, infectious, eosinophilic, pill, radiation), tylosis, diverticula, **iatrogenic** (post-surgery, radiation), esophageal ring/web, **extrinsic compression** (enlarged aorta, left atrium, mediastinal mass, lung cancer, lymphoma, osteophytes, subclavian artery)
- **MOTILITY**—achalasia, scleroderma, Chagas disease, diffuse esophageal spasm, hypertensive lower esophageal sphincter, nutcracker esophagus, non-specific esophageal motility disorders

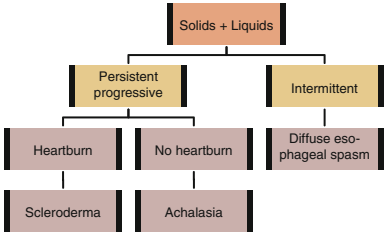
CLINICAL FEATURES

DIAGNOSTIC CLUES—history of heartburn may suggest GERD leading to erosive esophagitis, peptic stricture, or esophageal adenocarcinoma. History of atopic diseases especially in a young adult with recurrent dysphagia may suggest eosinophilic esophagitis. Also check for odynophagia, regurgitation, hematemesis, coffee ground emesis, respiratory symptoms, weight loss, and medication history (tetracycline, bisphosphonates, potassium supplements)

PRACTICAL APPROACH TO DYSPHAGIA
1. Features of oropharyngeal dysphagia (problems initiating swallowing, extending neck/arms when swallowing, changes in speech, coughing, choking, or nasal regurgitation)? Consider workup for oropharyngeal dysphagia. Otherwise, proceed to step 2
2. Difficulty swallowing both solids and liquids? If yes, consider motility disorders and proceed to step 3. If progressing from solids to liquids, consider structural disorders and proceed to step 4
3. For motility disorders, is the dysphagia progressive? If yes, consider achalasia or scleroderma. If intermittent, consider diffuse esophageal spasm or non-specific esophageal motility disorder
4. For structural disorders, is the dysphagia progressive? If yes, consider tumors and peptic stricture. If intermittent, consider esophageal ring
5. Any caustic ingestion history?

CLINICAL FEATURES (CONT'D)





INVESTIGATIONS

BASIC

- **IMAGING**—barium swallow (esophageal), videofluoroscopy (oropharyngeal)
- **SWALLOWING ASSESSMENT**—occupational therapy or speech pathology

SPECIAL

- **GASTROSCOPY**—for esophageal lesions and biopsy for eosinophilic esophagitis
- **ESOPHAGEAL MANOMETRY**—definitive for achalasia, useful for diffuse esophageal spasm
- **pH MONITORING**—for refractory GERD, especially if gastroscopy normal
- **FIBEROPTIC NASOPHARYNGEAL LARYNGOSCOPY**—for oropharyngeal dysphagia

MANAGEMENT

SYMPTOM CONTROL—postural/nutritional/behavioral modifications, swallowing rehabilitation, esophageal dilation

TREAT UNDERLYING CAUSE

SPECIFIC ENTITIES

ACHALASIA

- **PATHOPHYSIOLOGY**—a motor disorder with lack of peristalsis in the body of the esophagus and incomplete relaxation of the lower esophageal sphincter on manometry
- **DIAGNOSIS**—endoscopy is essential for ruling out malignancy ("pseudoachalasia"). Barium swallow (beak-like narrowing), esophageal manometry (definitive)
- **TREATMENTS**—endoscopic intrasphincteric injection of botulinum toxin, pneumatic dilation, and surgical myotomy

INFECTIOUS ESOPHAGITIS

- **PATHOPHYSIOLOGY**—common organisms include *Candida albicans*, CMV, and HSV. Happens more commonly in immunocompromised host
- **DIAGNOSIS**—gastroscopy and biopsy/viral cultures

EOSINOPHILIC ESOPHAGITIS

- **PATHOPHYSIOLOGY**—food allergens and genetic factors leading to eosinophilic infiltration and stricture (frequently presents in young males with esophageal foreign body)
- **DIAGNOSIS**—gastroscopy (esophageal trachealization) and biopsy
- **TREATMENTS**—control reflux, dilatation, dietary modification, fluticasone (administered as MDI and swallowed), and oral steroids (viscous budesonide slurry)

Related Topics
Esophageal Cancer (p. 215)
Stroke (p. 337)

Dyspepsia

DIFFERENTIAL DIAGNOSIS

NON-GASTRIC CAUSES—cardiac (myocardial infarction), pulmonary (pneumonia), hepatobiliary (biliary colic), pancreatic (pancreatitis), colonic (irritable bowel syndrome), musculoskeletal, dietary indiscretion

PEPTIC ULCER DISEASE (PUD, 10–20%)—*H. pylori*, ASA, NSAIDs (COX-2 inhibitors slightly decreased risk), cancer, Zollinger–Ellison, smoking

MEDICATION SIDE EFFECTS—NSAIDs, ASA, theophylline, calcium channel blockers, erythromycin, metronidazole, bisphosphonates, orlistat, acarbose, iron, potassium supplements

DIFFERENTIAL DIAGNOSIS (CONT'D)

GASTROESOPHAGEAL REFLUX DISEASE (GERD, 20%)

★ACIDS★

- **A**cid hypersecretion—Zollinger–Ellison disease
- **A**lcohol abuse
- **C**onnective tissue disease—scleroderma
- **I**nfections of esophagus—CMV, HSV, candidiasis
- **D**iabetic gastroparesis
- **D**rug therapy
- **S**moking

NON-ULCER DYSPEPSIA (50%)—cause unclear. Diagnosis of exclusion (rule out organic cause)

PATHOPHYSIOLOGY

COMPLICATIONS OF PUD—perforation, hemorrhage, gastric outlet obstruction, pancreatitis

COMPLICATIONS OF GERD—esophageal complications include esophagitis, esophageal ulcer, esophageal stricture, and Barrett's esophagus. Extra-esophageal complications include asthma, aspiration, chronic cough, hoarseness, chronic laryngitis, and dental erosions

CLINICAL FEATURES

SYMPTOM DEFINITIONS

- **DYSPEPSIA**—chronic or recurrent epigastric pain, often with regurgitation, heartburn, bloating, nausea, and post-prandial fullness (indigestion)
- **HEARTBURN**—retrosternal burning sensation secondary to lower esophageal sphincter relaxation = more specific for GERD

RATIONAL CLINICAL EXAMINATION SERIES: CAN THE CLINICAL HISTORY DISTINGUISH BETWEEN ORGANIC AND FUNCTIONAL DYSPEPSIA?

	LR+	LR–
Organic dyspepsia		
Diagnosis reached by the clinician or computer model	1.6	0.46
Peptic ulcer disease		
Diagnosis reached by the clinician or computer model	2.2	0.45
Esophagitis		
Diagnosis reached by the clinician or computer model	2.4	0.5

CLINICAL FEATURES (CONT'D)

APPROACH—"functional dyspepsia is defined as pain or discomfort centered in the epigastrium with a normal endoscopy. Neither clinical impression nor computer models that incorporated patient demographics, risk factors, history items and symptoms adequately distinguished between organic and functional disease in patients referred for endoscopic evaluation of dyspepsia"

JAMA 2006 295:13

PRACTICAL APPROACH TO DYSPEPSIA

1. Consider **non-gastric causes** of dyspepsia (cardiac, pulmonary, hepatobiliary, colonic, musculoskeletal, medications, and dietary indiscretion) and investigate those causes if likely. Otherwise proceed to step 2
2. If **age >50 or alarm symptoms ★Very BAD★** (**V**omiting, **B**leed/anemia, **A**bdominal mass/weight loss, **D**ysphagia), refer for gastroscopy to check for gastric cancer. Otherwise proceed to step 3
3. If **ASA or NSAIDs** use, stop medications if possible. If not, consider empiric proton pump inhibitor/H_2 blocker trial and proceed to step 4
4. If **GERD predominant symptoms** (heartburn, regurgitation), treat as GERD. Otherwise, proceed to step 5
5. If ***H. pylori*** **urea breath test positive**, treat with triple therapy. Otherwise, proceed to step 6
6. If none of the above, diagnosis of **non-ulcer dyspepsia**

Canadian Dyspepsia Working Group. Can J Gastroenterol 2005 19:5

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, glucose, AST, ALT, ALP, bilirubin, lipase, Ca, albumin
- **IMAGING**—upper GI series, US abd, CT abd

SPECIAL

- **UREA BREATH TEST**
- ***H. PYLORI* SEROLOGY**
- **24-H ESOPHAGEAL PH MONITORING**
- **ENDOSCOPY WITH BIOPSY**—urease test, C&S for *H. pylori*
- **PROTON PUMP INHIBITOR TEST**—sens 78% for GERD

MANAGEMENT

PEPTIC ULCER DISEASE—avoid NSAID use. Antisecretory treatment (*ranitidine* 150–300 mg PO BID, *omeprazole* 20–40 mg PO daily, *lansoprazole* 15–30 mg PO daily, *pantoprazole* 40 mg PO daily; all 30–60 min before meals; 8 week course). ***H. pylori* eradication** (★**CAO**★: *clarithromycin* 500 mg PO BID, *amoxicillin* 1 g PO BID, *omeprazole* 40 mg PO daily × 10 days; ★**CMO**★ (if penicillin allergy): *clarithromycin* 500 mg PO BID, *metronidazole* 250 mg PO QID, *omeprazole* 40 mg PO daily × 10 days; ★**BMT**★ (if macrolide allergy or failed first line): *bismuth* 30 mL PO QID, *metronidazole* 250 mg PO QID, *tetracycline* 500 mg PO QID × 2 weeks)

GERD—lifestyle changes (avoid coffee, alcohol, chocolate, high-fat meals, acidic or spicy foods. More frequent, smaller portions, exercise/weight loss, smoking cessation, elevate head of bed, loose garments). **Antisecretory treatment** (proton pump inhibitors more effective than H2 blockers for esophagitis. Use antacids as breakthrough). **Nissen fundoplication**

NON-ULCER DYSPEPSIA—lifestyle changes (avoid alcohol, caffeine, tobacco). **Antisecretory treatment** (see above). ***H. pylori* eradication** (may or may not relieve symptoms). **Promotility agent** (domperidone)

Related Topics
Esophageal Cancer (p. 215)
Gastric Cancer (p. 217)
Gastric Lymphoma (p. 193)

SPECIFIC ENTITIES

GERD

- **CAUSES**—obesity, lower esophageal sphincter pressure (transient relaxation of lower esophageal sphincter), decreased esophageal peristalsis, gastric acid hypersecretion, delayed gastric emptying, anatomic disruption lower esophageal sphincter (hiatal hernia)
- **PATHOPHYSIOLOGY**—reflux of stomach contents, leading to a multitude of symptoms including heartburn, regurgitation, dysphagia, chest pain, complicated by esophagitis, esophageal stricture, Barrett's esophagus, and esophageal adenocarcinoma
- **CLINICAL FEATURES**—esophageal (heartburn, regurgitation), extra-esophageal (wheeze, cough, pneumonia, waterbrash, hoarseness, sore throat, globus, dental erosions)

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—clinical based on symptoms (≥2/week). Endoscopy to look for complications and rule out other potential diagnoses

NEJM 2008 359:16

NSAIDS-INDUCED GASTROPATHY

- **PATHOPHYSIOLOGY**—NSAIDs inhibit COX-1 (normally protective effect through mucus secretion, bicarbonate secretion, mucosal circulation) and COX-2 (inducible inflammatory activity, also in kidneys). It also has direct toxic mucosal effect → dose related but even low dose baby ASA may contribute to ulcer formation. Overall ~20% patients on NSAIDs develop ulcers. Risk factors include age >60, preexisting peptic ulcer, multiple NSAIDs, high-dose NSAIDs, concomitant glucocorticoid or anticoagulant therapy
- **TREATMENTS**—primary prophylaxis includes proton pump inhibitor and misoprostol. If ulcer developed while on NSAIDs but must continue, should give proton pump inhibitor

BARRETT'S ESOPHAGUS

- **PATHOPHYSIOLOGY**—prolonged heartburn → intestinal squamous metaplasia (abnormal salmon-colored mucosa extending proximally from the gastroesophageal junction to the normal pale esophageal mucosa) → dysplasia → adenocarcinoma of esophagus and gastric cardia. Barrett's develops in 5–8% of patients with GERD. Transformation to low-grade dysplasia 4%/year, high-grade dysplasia 1%/year and cancer 0.5%/year
- **DIAGNOSIS**—screen with surveillance endoscopy every 2–3 years if age ≥50, white race, male, obese, chronic GERD, or presence of hiatal hernia. Mucosal biopsy after the initial diagnosis of Barrett's esophagus to look for dysplasia. Once diagnosed with Barrett's, endoscopy with biopsy every 3–5 years, 6–12 months if low-grade dysplasia
- **TREATMENTS**—high-grade dysplasia should be evaluated for esophagectomy, endoscopic mucosal resection, or ablative therapy

GASTROPARESIS

- **CAUSES**—systemic diseases (diabetes, scleroderma), drugs (anticholinergic agents, narcotics), idiopathic
- **PATHOPHYSIOLOGY**—impairment of gastric emptying due to dysfunction of the neuromuscular unit → dyspepsia, bloating, nausea, vomiting, and weight loss
- **DIAGNOSIS**—gastric emptying study, barium swallow, gastroscopy

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—frequent, small, low-fat, low-fiber feedings, prokinetic agents (*metoclopramide* 10 mg PO TID ac meals, *erythromycin* 250 mg PO TID ac meals, *domperidone* 10 mg PO QID), nutritional support

NEJM 2007 356:8

HELICOBACTER PYLORI

- **PATHOPHYSIOLOGY**—chronic inflammation → causative role in 50–80% of duodenal ulcers, 40–60% of gastric ulcers, 80% of gastric cancers, and 90% of gastric lymphomas

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—urea breath test (sens 90%, spc 95%. Particularly good in post-treatment setting; testing for eradication should be performed off antibiotic and proton pump inhibitor therapy), serology (sens 90%, spc 80%) is of limited value as it tests for IgG which only indicates previous exposure, endoscopy (culture, histologic assessment, urease testing)
- **TREATMENTS**—see H. PYLORI ERADICATION above

Acute Abdominal Pain

DIFFERENTIAL DIAGNOSIS

GI—peptic ulcer disease, pancreatitis, cholangitis, hepatitis, cholecystitis, inflammatory bowel disease, gastroenteritis, appendicitis, diverticulitis, bowel obstruction (small, large), volvulus
GU—pyelonephritis, renal colic, cystitis, prostatitis, testicular torsion, inguinal hernia
GYNECOLOGIC—ectopic pregnancy, ruptured ovarian cyst, pelvic inflammatory disease, fibroid torsion, endometriosis, endometritis
VASCULAR—acute mesenteric ischemia, ischemic colitis, chronic mesenteric ischemia, abdominal aortic aneurysm rupture
SYSTEMIC—Addison's disease, diabetic ketoacidosis, uremia, hypercalcemia, porphyria, familial Mediterranean fever
OTHERS—myocardial infarction, pneumonia, splenic injury, shingles, musculoskeletal, peritonitis

PATHOPHYSIOLOGY

CAUSES OF ABDOMINAL PAIN—any intra-abdominal organs (e.g. GI, GU, gynecological, spleen) × (ischemia, infection, obstruction, tumors) + systemic causes + referred pain

CLINICAL FEATURES

HISTORY—characterize abdominal pain (onset, location, duration, severity, radiation, aggravating and relieving factors), N&V, bleeding, fever, inquire about last menstrual period and pregnancy if female, past medical history (CAD, diabetes, hypertension, renal stones), past surgical history (abdominal adhesions), medication history (analgesics)
PHYSICAL—vitals, respiratory and cardiac examination, abdominal examination, CVA tenderness, pelvic and rectal examination
APPENDICITIS SEQUENCE—vague pain initially located in the epigastric or periumbilical region; anorexia, nausea, or non-sustained vomiting; migration of the initial pain to the RLQ; low-grade fever

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE APPENDICITIS?

	Sens	Spc	LR+	LR–
History				
Migration of pain to RLQ	64%	82%	3.18	0.5
RLQ pain	81%	53%	8.0	0.15
Pain before vomiting	100%	64%	2.76	–
No similar pain previously	81%	41%	1.5	0.32
Physical				
Rigidity	27%	83%	3.76	0.82
Fever	67%	79%	1.94	0.58
Rebound tenderness	63%	69%	3.7	0.4
Psoas sign	16%	95%	2.38	0.90
Obturator sign	–	–	–	–
Rectal exam	–	–	–	–

CLINICAL FEATURES (CONT'D)

	Sens	Spc	LR+	LR–
Combination of Findings				
Alvarado score ≥7	81%	74%	3.1	0.26

APPROACH—"migration of pain, RLQ pain and pain before vomit suggest appendicitis. Rigidity, positive psoas sign, fever and rebound tenderness increase likelihood of appendicitis. Absence of above and similar pain previously suggest appendicitis is less likely"

JAMA 1996 276:19

UPDATE—The Alvarado score (MANTRELS–**M**igration, **A**norexia-acetone, **Nausea-Vomiting**, **T**enderness RLQ [2 points], **R**ebound pain, **E**levation of temperature, **L**eukocytosis [2 points], **L**eft shift) is a user-friendly and powerful tool for assessing likelihood of acute appendicitis

The Rational Clinical Examination. McGraw-Hill, 2009

CLINICAL FEATURES (CONT'D)

DISTINGUISHING FEATURES BETWEEN PERITONITIS, SMALL BOWEL OBSTRUCTION, AND ABDOMINAL WALL PAIN

- **PERITONITIS**—rigidity (LR+ 5.1), guarding (LR+ 2.0), rebound tenderness (LR+ 2.0), positive cough test (LR+ 2.0). Other special tests include Rovsing's sign, psoas sign (flexion of hip against resistance increases abdominal pain), obturator sign (internal rotation of hip increases abdominal pain), and rectal/pelvic examination
- **SMALL BOWEL OBSTRUCTION**—visible peristalsis (LR+ 18.8), absent/tinkling/high-pitched bowel sounds (LR+ 5.0), abdominal bloating
- **ABDOMINAL WALL PAIN**—Carnett's test (palpate area of most intense tenderness while patient supine, then palpate again with patient half sitting up. If pain is intra-abdominal, the pain will not increase as tensed rectus muscles protect the underlying viscus)

Related Topic
Acute Pancreatitis (p. 156)

EXAMINATION OF ABDOMINAL MASSES

- **RIGHT UPPER QUADRANT MASS**—**liver** (downward with inspiration, left lobe, bruit/venous hum), **right kidney** (downward with inspiration, ballotable, palpable upper border), **gallbladder** (downward with inspiration, smooth and regular), **colon or gastroduodenal** (does not move with inspiration, ill-defined mass, high-pitch bowel sounds), **lymphoma** (does not move with inspiration, usually more central)

CLINICAL FEATURES (CONT'D)

- **LEFT UPPER QUADRANT MASS**—**spleen** (downward and medially with inspiration, notch, bruit), **left kidney** (downward with inspiration, ballotable, palpable upper border), **colon** (splenic flexure), **gastric or pancreatic** (ill-defined mass, difficult to clearly differentiate these masses on examination), **lymphoma** (does not move with inspiration, usually more central)
- **RIGHT LOWER QUADRANT MASS**—**colon, distal small bowel, or appendix** (lower GI masses are ill-defined and difficult to clearly differentiate on examination), **ovary, uterus, fallopian tube** (pelvic structures require bimanual examination), **lymphoma** (does not move with inspiration, usually more central)
- **LEFT LOWER QUADRANT MASS**—**colon, distal small bowel** (lower GI masses are ill-defined and difficult to clearly differentiate on examination), **ovary, uterus, fallopian tube** (pelvic structures require bimanual examination), **lymphoma** (does not move with inspiration, usually more central)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, lipase, amylase, lactate, INR, PTT, Ca, albumin, urinalysis, urine βhCG (if ♀ of reproductive age)
- **MICROBIOLOGY**—urine C&S, stool C&S
- **IMAGING**—CXR, AXR, US abd/pelvic

SPECIAL

- **IMAGING**—IVP, barium contrast, CT abd
- **ECG**—if suspect cardiac involvement
- **ENDOSCOPY**

DIAGNOSTIC ISSUES

APPROACH TO ABDOMINAL X-RAYS

- **FREE AIR**—pneumoperitoneum suggests perforation. Look for free air under right diaphragm on CXR view or R lateral decubitus view. On supine abd view, look for outline of bowel wall (normally can only see inside of lumen. If outside of bowel wall also seen, free air present)
- **SMALL BOWEL**—more central location, valvulae closer together, thin and cross completely. Dilated if >3 cm [1.2 in.], multiple air fluid levels suggest small bowel obstruction
- **LARGE BOWEL**—more peripheral location, colonic haustra wider apart, thick, and cross part way. Normally some air–fluid levels in ascending colon. Dilated if >5 cm [2 in.]. Thumb printing (mural edema) and dilated bowel suggest toxic megacolon. Check for air in bowel wall (pneumatosis intestinalis)
- **STOOL IN BOWEL**—cannot distinguish from abscess
- **KIDNEYS**—ureter runs along transverse processes. May see calculi along tract. If see kidney outline, suggests pneumoretroperitoneum
- **PSOAS**—air around psoas suggests perforated retroperitoneal structures (rectum, duodenum). Lack of psoas outline suggests retroperitoneal inflammation (decreased fat)
- **BILIARY STRUCTURES**—common bile duct up to 6 mm in size. Check for air in portal vein or common bile duct (bowel infarction)
- **OTHER STRUCTURES**—liver, spleen, bones

MANAGEMENT

ACUTE—ABC, O_2, IV hydration. **NPO**, NG if severe N&V/obstruction. ***Morphine*** 2.5–5 mg SC q3–4 h PRN and 1–2.5 mg IV q1h PRN. ***Dimenhydrinate*** 50 mg IM/IV q4h PRN

TREAT UNDERLYING CAUSE—early surgical consult if peritonitis. Empiric antibiotics if fever or suspect peritonitis (*ceftriaxone* 1 g IV q24h plus *metronidazole* 500 mg IV q8h, or *piperacillin-tazobactam* 3.375 g IV q6h, or *ciprofloxacin* 400 mg IV q12h plus *metronidazole* 500 mg IV q8h, or *meropenem* 1 g IV q8h)

SPECIFIC ENTITIES

GALLSTONE DISEASE SPECTRUM—asymptomatic (70%), biliary colic (20%, intermittent obstruction), acute cholecystitis (cystic duct obstruction), choledocholithiasis (common bile duct obstruction), ascending cholangitis (stasis and infection of biliary tract; may be secondary to choledocholithiasis; see p. 156 for more details), gallstone pancreatitis (pancreatic duct obstruction), gallstone ileus, gallbladder cancer

SPECIFIC ENTITIES (CONT'D)

ACUTE CHOLECYSTITIS

- **PATHOPHYSIOLOGY**—abnormalities of bile acid secretion, mucus generation, and gallbladder motility → gallstone formation → migrate to obstruct the cystic duct and even common bile duct/pancreatic duct → gallbladder inflammation and sometimes secondary infection → gallbladder necrosis and gangrene with perforation in severe cases. Risk factors include older age, obesity, fertility, women (i.e. **f**orty, **f**at, **f**ertile, **f**emale), ethnicity (Aboriginal, Hispanic), TPN, and rapid weight loss

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE ACUTE CHOLECYSTITIS?

HISTORY—RUQ pain, N&V, anorexia, fever

PHYSICAL—Murphy sign (arrest of inspiration while palpating the gallbladder during a deep breath), guarding, rigidity, RUQ mass, rebound, rectal tenderness

	Sens	Spc	LR+	LR–
Murphy sign	65%	87%	2.8	0.5
RUQ tenderness	77%	54%	1.6	0.4
Bedside US with gallstones and positive sonographic Murphy sign	–	–	2.7	0.13

INVESTIGATIONS—leukocytosis, ALP >120 U/L, elevated ALT or AST, elevated bilirubin

APPROACH—"no single clinical finding or laboratory test carries sufficient weight to establish or exclude cholecystitis without further testing (i.e. ultrasound). Clinical gestalt (without ultrasound) is estimated to have LR+ 25–30, bringing the probability of cholecystitis from 5% pretest to 60% post test. The evaluation of patients with abdominal pain suggestive of cholecystitis will continue to rely heavily on clinical gestalt and diagnostic imaging"

JAMA 2003 289:1

UPDATE—clinicians with training and experience in bedside ultrasound can visualize the gallbladder in most patients. For patients with low pretest probability of cholecystitis and definitively negative bedside ultrasound, formal ultrasound may not be required.

The Rational Clinical Examination. McGraw-Hill, 2009

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—US abd, endoscopic US, ERCP, percutaneous transhepatic cholangiography, MRCP, HIDA/DISIDA cholescintigraphy (acalculous cholecystitis), CT abd
- **TREATMENTS**—supportive measures include NPO, IV fluids, pain control (NSAIDs, opioids), antiemetics and antibiotics (*ceftriaxone* 1 g IV q24h plus *metronidazole* 500 mg IV q8h, or *piperacillin-tazobactam* 3.375 g IV q6h, or *ciprofloxacin* 400 mg IV q12h plus *metronidazole* 500 mg IV q8h, or *meropenem* 1 g IV q8h). Cholecystectomy (laparoscopic, open) or percutaneous cholecystostomy to facilitate drainage (if non-operative because of high risk). If biliary pain despite cholecystectomy, consider possibility of a retained common bile duct stone, sphincter of Oddi dysfunction, or functional pain

NEJM 2008 358:26

ACUTE MESENTERIC ISCHEMIA

- **PATHOPHYSIOLOGY**—embolism in the celiac or superior mesenteric artery from valvular heart disease or atrial fibrillation, thrombosis, or shock (low flow state) → sudden and severe periumbilical pain out of proportion with physical findings, N&V, leukocytosis, ↑ lactate, ileus

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—high clinical suspicion, CT abd (+ contrast). Angiography gold standard
- **TREATMENTS**—IV fluids, immediate surgery, anticoagulation if mesenteric arterial embolism or mesenteric venous thrombosis

ISCHEMIC COLITIS

- **PATHOPHYSIOLOGY**—low-flow state in the mesentery affecting mainly the "watershed" area of the middle colic and inferior mesenteric arteries → hematochezia, diarrhea, abdominal pain
- **DIAGNOSIS**—AXR ("thumbprinting" or edematous haustral folds), CT (focal or segmental bowel wall thickening or intestinal pneumatosis with portal vein gas), colonoscopy, laparoscopy
- **TREATMENTS**—supportive (hydration), antibiotics

CHRONIC MESENTERIC ISCHEMIA

- **PATHOPHYSIOLOGY**—↓ blood flow from atherosclerosis of the proximal mesenteric vessels → intestinal angina with post-prandial abdominal pain → fear of eating, extensive weight loss
- **DIAGNOSIS**—CT abdomen/pelvis (initial), mesenteric duplex US (sens 90% for stenosis of >50%), CT angiography
- **TREATMENTS**—angioplasty, surgical revascularization, management of vascular risk factors

Upper GI Bleed — NEJM 2008 359:9

DIFFERENTIAL DIAGNOSIS

PEPTIC ULCER DISEASE (PUD)—gastric, duodenum
INFLAMMATION—**esophagitis** (CMV, medications), **gastritis** (acute, chronic), **inflammatory bowel disease** (Crohn's)
VARICES—esophagus, stomach
TUMORS—esophagus, stomach, duodenum
STRUCTURAL—Mallory–Weiss tear, Boerhaave's syndrome, Dieulafoy's lesion, arteriovenous malformation, aortoduodenal fistula, hemobilia
OTHERS—epistaxis, hemoptysis

CLINICAL FEATURES

HISTORY—volume of hematemesis, melena, and hematochezia, vomiting, past medical history

CLINICAL FEATURES (CONT'D)

(PUD, *H. pylori* infection, alcohol-related disorders, liver cirrhosis with varices, renal failure, metastatic cancer, heart disease/HF), medication history (anticoagulants, NSAIDs)
PHYSICAL—acute bleeding, sinus tachycardia, supine hypotension (SBP <95 mmHg), postural pulse increase >30/min or dizziness, anemia (conjunctival, facial or palmar pallor), cirrhosis (facial telangiectasia, palmar erythema, spider angiomas, gynecomastia, abdominal wall veins, Terry's nails/leukonychia, peripheral edema). Perform a rectal examination and test for fecal occult blood. Examine vomitus or nasogastric aspirate and test for occult blood
BLACK STOOL THAT MAY MIMIC MELENA—bismuth subsalicylate, iron, spinach, charcoal

CLINICAL FEATURES (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE A SEVERE UPPER GASTROINTESTINAL BLEED?

	LR+	LR–
Clinical Factors Distinguishing UGIB vs. LGIB		
Prior history of UGIB	6.2	0.81
Age <50 years	3.5	0.80
Cirrhosis	3.1	0.97
History of melena	5.1–5.9	0.06–0.27
Melenic stool on examination	25	0.52
Nasogastric lavage with blood or coffee grounds	9.6	0.58
Clots in stool	0.05	1.2
Serum urea nitrogen:creatinine ratio >30	7.5	0.53
Clinical Factors Determining Need for Urgent Evaluation of UGIB		
History of malignancy or cirrhosis	3.7	0.83
Cirrhosis	3.2	0.89
Syncope	3.0	0.95
Pulse rate >100/min	4.9	0.34
Nasogastric lavage with red blood	3.1	0.32
Hemoglobin level <8 g/dL	4.5–6.2	0.36–0.41
Serum urea nitrogen >90 mg/dL	3.6	0.45
Blatchford score = 0	1.2	0.02

BLATCHFORD SCORE: determined by blood urea, hemoglobin, systolic blood pressure, pulse > 99 beats/min, presentation with melena, presentation with syncope, hepatic disease, cardiac failure

APPROACH—"tachycardia (pulse rate of >100/min; LR, 4.9), a history of cirrhosis or malignancy (LR+ 3.7), hemoglobin level of less than 8 g/dL (LR+ range, 4.5-6.2), or a nasogastric lavage with red blood (LR+ 3.1) increase the likelihood of severe bleeding. All patients with a UGIB should have a Blatchford score, which does not require a nasogastric lavage, to help assess the severity (Blatchford score = 0; LR- 0.02 for identifying patients requiring urgent evaluation). When negative, prediction rules combining symptoms, signs, and routine laboratory test results almost definitively rule out severe UGIB, thereby identifying at least some patients who can be safely evaluated as an outpatient"

JAMA 2012 307:10

CLINICAL FEATURES (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES: IS THIS PATIENT HYPOVOLEMIC? HYPOVOLEMIA DUE TO ACUTE BLOOD LOSS

	Sens	Spc
For moderate blood loss		
Postural pulse increment ≥30/min or severe postural dizzines	22%	–
Postural hypotension ≥20 mmHg SBP drop	9%	94%
Supine tachycardia	0%	96%
Supine hypotension	13%	97%
For large blood loss		
Postural pulse increment ≥30/min or severe postural dizziness	97%	98%
Supine tachycardia	12%	96%
Supine hypotension	33%	97%

NOTE: postural change is measured first with supine vitals counting pulse for 30 s (after waiting 2 min), then standing vitals (after waiting 1 min)

JAMA 1999 281:11

Related Topic
Shock (p. 108)

CLINICAL FEATURES (CONT'D)

HYPOVOLEMIA DUE TO VOMITING, DIARRHEA, DECREASED INTAKE, DIURETICS

	Sens	Spc	LR+	LR–
Symptoms				
Postural pulse increment ≥30/min	43%	75%	1.71	0.8
Postural hypotension ≥20 mmHg	29%	81%	1.5	0.9
Dry axilla	50%	82%	2.8	0.6
Dry oral/nasal mucous membrane	85%	58%	2.0	0.3
Dry tongue	59%	73%	2.1	0.6
Tongue with furrows	85%	58%	2.0	0.3
Sunken eyes	62%	82%	3.4	0.5
Confusion	57%	73%	2.1	0.6
Upper/lower extremity weakness	43%	82%	2.3	0.7
Speech not clear or expressive	56%	82%	3.1	0.5
Capillary refill time > normal	34%	95%	6.9	0.7

APPROACH—"for patients with suspected acute blood loss, severe postural dizziness (preventing upright vitals measurements) or postural pulse increment are predictive. Postural hypotension has no incremental value. For patients with suspected hypovolemia not due to blood loss, severe postural dizziness, postural pulse increment, or dry axilla can be helpful. Moist mucous membranes and tongue without furrows argue against it. Capillary refill time and poor skin turgor have no proven diagnostic value"

JAMA 1999 281:11

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, type/cross-match, PTT, INR, AST, ALT, ALP, bilirubin, albumin, fecal occult blood
- **IMAGING**—CXR, AXR
- **GASTROSCOPY**

PROGNOSTIC ISSUES

RISK STRATIFICATION FOR PEPTIC ULCER DISEASE

- **CLINICAL ROCKALL SCORING**—age 60–79 = 1; age ≥80 = 2; heart rate >100 beats/min = 1; systolic BP <100 mmHg = 2; co-existing illnesses (ischemic heart disease, HF, other major illness) = 2; co-existing illnesses (renal failure, hepatic failure, metastatic cancer) = 3
- **COMPLETE ROCKALL SCORING**—in addition to clinical Rockall score, add the following based on endoscopic findings: no lesion observed, Mallory–Weiss tear = 0; peptic ulcer, erosive disease, esophagitis = 1; cancer of upper GI tract = 2; clean base ulcer, flat pigmented spot = 0; blood in upper GI tract, active bleeding, visible vessel, clot = 2
- **INTERPRETATION**—low risk for bleeding or death = clinical Rockall score 0 or complete Rockall score ≤2

PROGNOSTIC ISSUES (CONT'D)

RISK OF ULCER RE-BLEED

- **HIGH-RISK FEATURES**—active spurting/oozing during endoscopy (90% chance), non-bleeding visible vessel (50% chance), adherent clot (25–30% chance). If none of above factors and clinically not severe bleed, very low chance of rebleed and may consider discharging shortly after. Other factors include size and location of ulcer
- **LOW-RISK FEATURES**—flat spot (10% chance), clean ulcer base (3–5% chance)

MANAGEMENT

ACUTE—**ABC**, O_2, **IV hydration** (two large-bore IVs). **Transfusion** (especially if hemoglobin <70 g/L [<7 g/dL], platelets $<50 \times 10^9$). NPO, consider NG tube. **Hold** antihypertensive and diuretic therapy. If prolonged PT/PTT, ***vitamin K*** 10 mg IV (small risk of anaphylaxis) and ***FFP*** 2–4 U IV or ***unactivated prothrombin complex concentrates (PCC)*** 1000–3000 U IV (dosing based on INR and severity of bleeding), if rapid reversal required. If on heparin, consider ***protamine*** infusion (1 mg antagonizes 100 U of heparin—beware of excessive protamine which can cause paradoxical coagulopathy). If suspect varices, ***octreotide*** 50 μg IV bolus, then 25–50 μg/h. ***Pantoprazole*** 80 mg IV bolus, then 8 mg/h until endoscopy. If cirrhosis and acute variceal hemorrhage, **transfuse** platelet and FFP PRN, antibiotics for 7 days (*ceftriaxone*

MANAGEMENT (CONT'D)

1 g IV q24h, *cefotaxime* 1 g IV q8h, *ciprofloxacin* 400 mg IV q12h, *ciprofloxacin* 500 mg PO BID, or *norfloxacin* 400 mg PO BID). **Consult GI** for gastroscopy and consider ***erythromycin*** 250 mg IV 30–90 min before endoscopy for clot lavage

TREAT UNDERLYING CAUSE—**avoid** ASA, NSAIDs. **Peptic ulcer** (endoscopic hemostasis with thermal coagulation/fibrin sealant/endoclips plus 1:10,000 ratio epinephrine injection. After endoscopy, start *pantoprazole* 80 mg IV bolus if not given already, then 8 mg/h × 72 h [if high-risk lesion], switch to 40 mg PO BID × 1 month then daily). **Varices** (endoscopy within 12 h with ligation/band/glue/sclerotherapy → balloon tamponade → transjugular intrahepatic portosystemic shunt (TIPS) → portacaval/distal splenorenal shunt, or liver transplant. Continue octreotide for 3 days. Repeat endoscopy every 2–4 weeks until varices obliterated, then at 1–3 months and again every 6–12 months afterward. Consider non-selective β-blocker such as *nadolol* 40–80 mg PO daily or *propranolol* 20 mg PO BID. **Mallory–Weiss tear** (*omeprazole* 20 mg PO daily). ***H. pylori*** eradication (see DYSPEPSIA p. 125 for treatment). **Intractable or recurrent bleed** (consult surgery. See TREATMENT ISSUES below)

MANAGEMENT (CONT'D)

TREATMENT ISSUES

CRITERIA FOR SURGICAL CONSULT FOR ULCER BLEED—hemodynamic instability despite resuscitation (>3 U PRBC), shock, recurrent hemorrhage after two endoscopic attempts, continued slow bleed requiring >3 U PRBC/day), high-risk endoscopic lesion

COMPLICATIONS OF ENDOSCOPY—perforations, bleeding, sedation-related respiratory failure

DISCHARGE DECISIONS FOR PATIENTS' PEPTIC ULCER DISEASE—patients with low-risk of rebleed (complete Rockall score ≤2, low risk endoscopic features), with Hb >80–100 g/L [>8–10 g/dL] without further need of transfusions, normal INR/PTT, and have adequate social support may be safely discharged home shortly after endoscopy with follow-up, while patients with high-risk features should be admitted and monitored closely

Lower GI Bleed

DIFFERENTIAL DIAGNOSIS

UPPER GI SOURCE WITH BRISK BLEEDING (10%)

INFECTIOUS—*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *E. coli* (EHEC, EIEC), *C. difficile*, *Amoeba*

TUMORS—colorectal cancer, small bowel cancer, polyp

INFLAMMATORY—inflammatory bowel disease (IBD)

ISCHEMIC—ischemic colitis

STRUCTURAL—angiodysplasia, diverticulosis, radiation colitis, hemorrhoids, anal fissure, intussusception, Meckel's diverticulum

CLINICAL FEATURES

HISTORY—volume of bleed, melena, abdominal pain, past medical history (IBD, cancer, diverticulosis), medication history (anticoagulants, antiplatelet drugs, NSAIDs)

PHYSICAL—acute bleeding, sinus tachycardia, supine hypotension (SBP <95 mmHg), postural pulse increase >30/min or dizziness, anemia (conjunctival, facial or palmar pallor), abdominal tenderness. Perform a rectal examination and test for fecal occult blood

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, type/X-match, PTT, INR, AST, ALT, ALP, bilirubin, albumin
- **MICROBIOLOGY**—stool C&S, fecal occult blood
- **ENDOSCOPY**—colonoscopy, gastroscopy

SPECIAL

- **IMAGING**—for obscure bleed, consider ^{99}Tc RBC scan (detects 0.1 mL/min), angiography (detects 0.5 mL/min), capsule endoscopy, push enteroscopy, double balloon enteroscopy, MR enterography and/or Meckel's scan

DIAGNOSTIC ISSUES

OCCULT BLEED—no obvious melena or bright red blood per rectum (BRBPR), but possible bleed as fecal occult blood or fecal immunochemical test positive

OBSCURE BLEED—obvious bleeding but source cannot be found

OVERALL APPROACH—gastroscopy and/or colonoscopy (start with the end with the most likely source of bleed, then scope the other end if no yield) → if negative, repeat panendoscopy → if negative, small bowel

DIAGNOSTIC ISSUES (CONT'D)

follow-through → if negative, consider angiography, RBC scan, capsule, push or double balloon endoscopy, or laparotomy

MANAGEMENT

ACUTE—ABC, O_2, **IV hydration** (two large-bore IVs). **Transfusion** (especially if hemoglobin <70 g/L [<7 g/dL], platelets $<50 \times 10^9$/L). NPO. **Hold** antihypertensive and diuretic therapy. If prolonged

MANAGEMENT (CONT'D)

PT/PTT, ***vitamin K*** 10 mg IV (small risk of anaphylaxis) [see above comment for UGIB] and ***FFP*** 2–4 U IV or ***unactivated prothrombin complex concentrates (PCC)*** 1000–3000 U IV (dosing based on INR and severity of bleeding), if rapid reversal required. If on unfractionated heparin, ***protamine*** infusion (1 mg antagonizes 100 U of heparin). **Consult GI** for endoscopy

TREAT UNDERLYING CAUSE

Inflammatory Bowel Disease Exacerbation

DIFFERENTIAL DIAGNOSIS

SEE DIFFERENTIAL DIAGNOSIS FOR ACUTE ABDOMINAL PAIN (p. 128) **LOWER GI BLEED** (p. 134) and **CHRONIC DIARRHEA** (p. 138)

PATHOPHYSIOLOGY

TYPES

- **CROHN'S—mild to moderate** (relatively asymptomatic, tolerating oral diet), **moderate to severe** (failed treatment for mild disease, symptomatic), **severe to fulminant** (failed steroid treatment, very symptomatic)
- **ULCERATIVE COLITIS—ulcerative proctitis** (limited to rectum), **distal colitis/protosigmoiditis** (extending up to mid-sigmoid colon), **left-sided colitis** (extending up to splenic flexure), **extensive colitis** (extending up to but not including cecum), **pancolitis** (extending up to cecum)

CLINICAL FEATURES

EXTRAINTESTINAL MANIFESTATIONS—fever, clubbing, uveitis, iritis, anemia, jaundice (primary sclerosing cholangitis), aphthous ulcers (Crohn's only), arthritis (spondylitis; type I arthropathy: pauciarticular and related to IBD activity; type II arthropathy: polyarticular and unrelated to IBD activity), erythema nodosum, pyoderma gangrenosum, DVT, amyloidosis

CLINICAL FEATURES (CONT'D)

DISTINGUISHING FEATURES BETWEEN CROHN'S DISEASE AND ULCERATIVE COLITIS

	Crohn's disease	Ulcerative colitis
Degree of involvement	Segmental ("skip lesions") Rectal sparing	Continuous
Symptoms	Abd pain Diarrhea Anorexia Perianal disease	Bloody diarrhea Tenesmus Fever
Serology	Anti-*Saccharomyces cerevisiae* IgG antibody (sens 77%, spec 92%, PPV 82%)	p-ANCA (sens 70%, spc 88%, PPV 75%)
Pathology	Transmural granuloma	Mucosal inflammation No granulomas
Complications	Obstruction Strictures Fistulas Fissures Abscesses Colorectal cancer	Toxic megacolon (1–2%) Colorectal cancer (1%/year after 10 years)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, ESR, CRP, Fe, TIBC, ferritin, % sat, AST, ALT, ALP, bilirubin, albumin, Ca, Mg, PO_4, vitamin B12, folate, fecal calprotectin, fecal lactoferrin
- **MICROBIOLOGY**—stool C&S, fecal occult blood, stool for *C. difficile* toxin assay
- **SEROLOGY**—antineutrophil cytoplasmic antibodies (pANCA), anti-*Saccharomyces cerevisiae* antibodies (ASCA)
- **IMAGING**—AXR, CT/MR enterography, contrast-enhanced US
- **ENDOSCOPY**—flexible sigmoidoscopy, colonoscopy, double-balloon enteroscopy

MANAGEMENT

SUPPORTIVE THERAPY

- **DIET AND NUTRITION**—if mild, low-fiber diet, elemental diet; if severe, TPN and bowel rest
- **ANTIDIARRHEAL AGENTS**—contraindicated in severe exacerbation and toxic megacolon

ANTIINFLAMMATORY AGENTS

- **5ASA SUPPOSITORIES**—if localized (i.e. rectal/left-sided) disease. *Mesalamine* 1 g PR qhs, glucocorticoid enema/suppositories daily-BID
- **SYSTEMIC 5ASA**—for induction and maintenance (*sulfasalazine* induction 0.5 g PO BID, then titrate to 0.5–1.5 g PO QID, maintenance 1 g PO BID–QID; *mesalamine* 800–1600 mg PO TID maintenance 400–800 mg PO TID; *olsalazine*)
- **GLUCOCORTICOIDS**—for flares (*methylprednisolone* 30 mg IV BID, *prednisone* 50 mg PO daily, reduce by 5 mg/week)
- **IMMUNOSUPPRESSIVE AGENTS**—*azathioprine* 50 mg PO daily, increase by 25 mg daily every 2 weeks to a max of 2–2.5 mg/kg/day as tolerated (monitor CBC, liver enzymes), *methotrexate* 25 mg IM weekly
- **ANTIBIOTICS**—*metronidazole* 500 mg PO TID, *ciprofloxacin* 500 mg PO BID
- **BIOLOGICAL AGENTS**—*infliximab* IV infusions of 5 mg/kg at 0, 2, 6 weeks, followed by 5–10 mg/kg every 8 weeks for maintenance; or *adalimumab* 160 mg SC initially then 80 mg SC at 2 weeks, 40 mg SC at 4 weeks, followed by 40 mg SC every other week for maintenance. Drug coverage for anti-TNF therapy differs between Canadian provinces

MANAGEMENT (CONT'D)

SURGERY

Related Topics
Clostridium difficile Colitis (p. 137)
Inflammatory Arthritis (p. 321)

TREATMENT ISSUES

CROHN'S COLITIS

- **STEPWISE TREATMENT**—oral 5ASA or sulfasalazine for 3–4 weeks. If failed, add metronidazole and ciprofloxacin. If failed, add oral steroids for 4 weeks. If failed, consider immunosuppressive therapy. Consider metronidazole and ciprofloxacin, biologic therapy for treatment of perianal fistula

ULCERATIVE COLITIS

- **ULCERATIVE PROCTITIS**—5ASA suppositories or enemas for 2–4 weeks for active treatment. If failed, add steroid foams. Consider oral 5ASA if patient cannot tolerate suppositories. Maintenance therapy may be required
- **DISTAL COLITIS/PROTOSIGMOIDITIS AND LEFT-SIDED COLITIS**—similar treatment to ulcerative proctitis, push to maximal dose if necessary. If failed, add budesonide enemas. If failed, add oral prednisone. Maintenance therapy is recommended
- **EXTENSIVE AND PANCOLITIS** (mild-moderate)—oral 5ASA or sulfasalazine, plus topical 5ASA or steroid enemas. Add oral prednisone if failed or severe symptoms. Maintenance therapy is required
- **EXTENSIVE AND PANCOLITIS** (severe)—hospitalize with bowel rest, hydration, nutrition, parenteral steroids, and adjunctive rectal and oral therapy. Consider adding metronidazole, ciprofloxacin, and infliximab or cyclosporine. May need surgical consult

TOXIC MEGACOLON

- **PATHOPHYSIOLOGY**—a potential complication of inflammatory bowel disease, infectious colitis (*C. difficile*, other inflammatory organisms), ischemic colitis, and obstructive colon cancer
- **CLINICAL FEATURES**—the combination of abdominal distension and diarrhea (may be bloody) should prompt investigations for toxic megacolon. Patient usually toxic with fever, hypotension, delirium, and abdominal pain

TREATMENT ISSUES (CONT'D)

- **DIAGNOSIS**—**dilated colon on X-ray** (usually transverse or right colon, >6 cm), plus **three of the following** (fever >38 °C [100.4 °F], tachycardia >120/min, leukocytosis $>10.5 \times 10^9$/L, anemia), plus **one of the following** (dehydration, delirium, electrolyte disturbances, hypotension)
- **TREATMENTS**—supportive therapy (NPO, IV fluids, hold all opioids, antidiarrheal and anticholinergic agents). For IBD-related toxic megacolon, give *hydrocortisone* 100 mg IV q6h and antibiotics (ceftriaxone plus metronidazole). For *C. difficile*-related toxic megacolon, treat aggressively with IV metronidazole and PO/NG vancomycin. Patients with toxic megacolon who do not respond to therapy within 72 h should be considered for colectomy. ICU admission for monitoring. Serial blood tests and AXR daily to assess progress

TREATMENT ISSUES (CONT'D)

Acute Diarrhea NEJM 2004 350:1

DIFFERENTIAL DIAGNOSIS

INFLAMMATORY/INVASIVE (fever, bloody diarrhea, tenesmus)

- **INVASIVE INFECTIONS**—*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, EHEC, EIEC, *Vibrio parahaemolyticus*, *Clostridium difficile*, *Entamoeba*
- **INFLAMMATORY**—ulcerative colitis, Crohn's
- **ISCHEMIC COLITIS**
- **RADIATION COLITIS**

NON-INFLAMMATORY

- **NON-INVASIVE INFECTIONS**—**bacterial** (*Vibrio cholera*, *Staphylococcus aureus*, *Bacillus cereus*, *Clostridium perfringens*, *C. difficile*, ETEC, EPEC), **viral** (Rotavirus, norovirus, CMV), **parasites** (*Giardia*, *Cryptosporidium*, *Amoeba*)
- **MEDICATIONS**—antibiotics, laxatives, chemotherapy

PATHOPHYSIOLOGY

DEFINITION OF DIARRHEA—3 bowel movements/day or at least 200 g of stool/day. Acute diarrhea is defined as <2 weeks, whereas chronic diarrhea is defined as ≥2 weeks duration

DIARRHEA AND ASSOCIATED SYNDROMES

- ***SALMONELLA***—may cause septicemia in patients with sickle cell anemia or AIDS
- ***SHIGELLA***—precedes reactive arthritis
- ***CAMPYLOBACTER***—precedes 10–30% of Guillain–Barre syndrome
- ***YERSINIA***—mesenteric adenitis, erythema nodosum, polyarthritis, reactive arthritis, bacteremia, may mimic appendicitis

DIARRHEA AT VARIOUS SETTINGS

- **COMMUNITY ACQUIRED**—*Salmonella* (prevalence 16/100,000), *Campylobacter* (13/100,000), *Shigella* (10/100,000), *E. coli* O157:H7 (1.7/100,000), *Cryptosporidium* (1.4/100,000)

PATHOPHYSIOLOGY (CONT'D)

- **TRAVELER'S**—ETEC
- **NOSOCOMIAL**—*C. difficile*
- **PERSISTENT DIARRHEA** (>7 days)—*Giardia*, *Isospora belli*, *Cyclospora*, *Cryptosporidium*
- **IMMUNOCOMPROMISED**—*Microsporidia*, MAC, CMV

NATURAL HISTORY—most diarrheal illnesses are self-limited or viral-induced and nearly 50% last <1 day

CLINICAL FEATURES

HISTORY—characterize diarrhea (duration, frequency, volume, blood, floating), infectious contacts, recent food intake, abdominal pain, past medical history (IBD, lactose intolerance), medication history (laxatives, antibiotics), travel history

PHYSICAL—vitals and check for dehydration. Abdominal tenderness. Perform a rectal examination. Inspect stool sample if available

SALMONELLA* AND *CAMPYLOBACTER—although they are classified as inflammatory, patients usually only develop fever and severe diarrhea and not bloody diarrhea

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, lactate
- **MICROBIOLOGY**—stool C&S (sens 1.5–5.6%), O&P, C. diff toxin A + B, viral culture

SPECIAL

- **FECAL TESTING**—fecal leukocytes (inflammatory, sens 73%, spc 84%), fecal lactoferrin (inflammatory, sens 92%, spc 79%), Giardia toxin, fecal occult blood
- **ENDOSCOPY**—flexible sigmoidoscopy, colonoscopy

MANAGEMENT

SYMPTOM CONTROL—IV hydration. Antidiarrheal agents if not inflammatory (*bismuth subsalicylate* 2 tab PO q1h PRN or *loperamide* 4 mg × 1 dose, then 2 mg PO PRN, maximum 16 mg/day)

TREAT UNDERLYING CAUSE—*Shigella, Salmonella, Campylobacter, E. coli* other than EHEC (*ciprofloxacin* 500 mg PO BID × 3 days, *levofloxacin* 500 mg PO daily × 3 days). ***Vibrio cholera*** (*tetracycline* 500 mg PO QID × 3 days, *doxycycline* 300 mg PO × 1 dose, or *azithryomycin* 1 g PO × 1 dose). ***Isospora* and *Cyclospora*** (*trimethoprim–sulfamethoxazole* 160/800 PO BID × 7–10 days). ***C. difficile, Giardia,* and *Entamoeba*** (*metronidazole* 500 mg PO TID × 10 days)

Related Topic
Acute Abdominal Pain (p. 128)

SPECIFIC ENTITIES

ANTIBIOTICS-ASSOCIATED DIARRHEA AND PSEUDOMEMBRANOUS COLITIS

- **PATHOPHYSIOLOGY**—organisms include *C. difficile* (particularly with clindamycin, cephalosporins, penicillins) and non-*C. difficile* organisms (*Salmonella*, *C. perfringens*, *S. aureus*, *Candida*). Relapse occurs in 20–25% of patients and typically between 3 and 21 days after discontinuation of treatment: 3–5% of patients have more than 6 relapses. Note emergence of virulent *C. difficile* strain NAP-1/027 characterized by increased secretion of toxins A/B, binary toxin production and fluoroquinolone resistance, and associated with increased outbreaks and mortality
- **RISK FACTORS**—onset of diarrhea ≥6 days after the initiation of antibiotic therapy, hospital stay ≥2 weeks, fecal leukocytes, semi-formed stools, cephalosporin use

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—usually watery diarrhea (may be bloody if severe colitis), abdominal pain. In patients with severe *C. difficile* infection, significant leukocytosis, pseudomembranous colitis, toxic megacolon (see p. 135), acute renal failure, and hypotension may develop
- **DIAGNOSIS**—*C. difficile* toxin A/B from stool sample, flexible sigmoidoscopy (pseudomembranous colitis). *C. difficile* toxin levels are usually unnecessary immediately after treatment completion as up to one-third of patients have positive assays despite successful treatment
- **TREATMENTS**—**IV hydration. Discontinue** implicated antibiotics. **Avoid** use of antiperistaltic agents (opiates, loperamide). ***C. difficile* treatment** (*metronidazole* 250 mg PO QID × 10–14 days, *metronidazole* 500 mg PO TID × 10–14 days, or *vancomycin* 125–500 mg PO QID × 10–14 days). For severe cases, consider oral vancomycin as first-line agent. If significant ileus or toxic megacolon, give vancomycin via NG or enema and *add* metronidazole 500 mg IV QID. Avoid repeating stool assays after treatment unless patient has moderate or severe diarrhea. A positive *C. difficile* toxin without significant symptoms should not prompt treatment. For ***C. difficile* recurrence**, consider retreatment with 14-day course and minimize use of other antibiotics. For further recurrences, consider tapering doses of *vancomycin* 125 mg PO QID × 1 week, then BID × 1 week, then daily × 1 week, then every other day × 1 week, then every 3 days × 2 weeks. Alternatives include *vancomycin* 125 mg PO QID in combination with *rifampin* 600 mg BID × 7 days, or *Saccharomyces boulardii* 250 mg PO QID in combination with metronidazole or vancomycin, or *fidaxomicin* 200 mg PO BID × 10 days

NEJM 2002 346:5; NEJM 2008 359:18

Chronic Diarrhea

NEJM 1995 332:11

DIFFERENTIAL DIAGNOSIS

★MISO★

MOTILITY—hyperthyroidism, diabetic neuropathy, bacterial overgrowth, irritable bowel syndrome (IBS), scleroderma

INFLAMMATORY

- **INFECTIONS**—*Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *E. coli* (EHEC, EIEC), *C. difficile*, Amoeba

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **INFLAMMATORY**—ulcerative colitis, Crohn's, ischemic, radiation, toxic

SECRETORY

- **INFECTIONS**—Cholera, *Staphylococcus*, *B. cereus*, *C. perfringens*, *E. coli* (ETEC, EPEC), Rotavirus, norovirus, CMV, Giardia, Cryptococcus, Amoeba

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **NEUROENDOCRINE TUMORS**—carcinoid, VIPoma, calcitonin excess, gastrinoma, somatostatinoma
- **MEDICATIONS**—laxatives
- **OTHERS**—bile salt enteropathy, fatty acid induced, collagenous colitis, lymphocytic colitis

OSMOTIC

- **MALDIGESTION/MALABSORPTION**—pancreatic insufficiency, celiac disease, lactose intolerance, short bowel syndrome, enteric fistula
- **MEDICATIONS**—antacids, antibiotics, Mg citrate, Mg hydroxide, lactulose, sorbitol (i.e. "chewing gum diarrhea"), colchicine, metformin

Related Topics
Inflammatory Bowel Disease (p. 135)
Irritable Bowel Syndrome (p. 142)

CLINICAL FEATURES

HISTORY—characterize diarrhea (duration, frequency, volume, blood, floating), infectious contact, abdominal pain, weight loss, past medical history (diabetes, hyperthyroidism, IBS, lactose intolerance, bowel surgery, scleroderma), medication history (laxatives)

PHYSICAL—obtain body weight and inspect stool sample. Abdominal tenderness. Perform a rectal examination and test for fecal occult blood

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, albumin, TSH, antitransglutaminase antibody, endomysial antibody
- **MICROBIOLOGY**—stool C&S, O&P, C. diff toxin A + B, Giardia toxin

SPECIAL

- **FECAL TESTING**—fecal leukocytes, fecal fat, fecal lytes, fecal occult blood, stool for phenothalin (laxative abuse), α-1 antitrypsin
- **IMAGING**—SBFT, CT abd
- **ENDOSCOPY**—upper and lower, for biopsy

INVESTIGATION ISSUES

DISTINGUISHING FEATURES

- **INFLAMMATORY**—bloody stool, fecal leukocytes
- **SECRETORY**—fecal osmotic gap <50 mOsm/kg, >500 g of stool with fasting

INVESTIGATION ISSUES (CONT'D)

- **OSMOTIC**—fecal osmotic gap >50 mOsm/kg; <500 g of stool with fasting

FECAL OSMOTIC GAP—280 − 2 × (stool Na + K)

MANAGEMENT

SYMPTOM CONTROL—**hydration** and **nutritional support**. Empiric treatment with **antidiarrheal** agents if not inflammatory (*bismuth subsalicylate* 2 tab PO q1h PRN or *loperamide* 4 mg × 1 dose, then 2 mg PO PRN, maximum 16 mg/day)

TREAT UNDERLYING CAUSE—cholestyramine for bile acid-induced diarrhea

SPECIFIC ENTITIES

CELIAC DISEASE

- **PATHOPHYSIOLOGY**—sensitivity to gluten in **B**arley, **R**ye, **O**at, **W**heat ★**BROW**★ → T-cell-mediated immune reaction to gliadin → intestinal epithelial cell death → villous atrophy, crypt hyperplasia → malabsorption in small bowel. More common in females (2–3:1). Associated with type 1 diabetes, dermatitis herpetiformis (p. 409), IgA deficiency, liver dysfunction, and small bowel lymphoma (especially if no response to celiac diet)
- **CLINICAL FEATURES**—abdominal bloating (especially after inadvertent ingestion of gluten), isolated weight loss, iron-deficiency anemia in the absence of gastrointestinal blood loss, nutritional deficiency, osteoporosis (sometimes osteomalacia), diarrhea (sometimes), liver dysfunction
- **DIAGNOSIS**—antitransglutaminase IgA (sens 94%, spc 99%), antiendomysial IgA, antigliadin IgG (celiac patients with IgA deficiency may not be antitransglutaminase positive). Small bowel biopsy recommended for confirmation of diagnosis (intraepithelial lymphocytosis, crypt hyperplasia, villous atrophy, and good response to gluten-free diet). HLA DQ2 (~95%) and HLA DQ8 (~5%) may be present (absence of both DQ2/DQ8 makes celiac disease highly unlikely). Once diagnosed, a bone mineral density scan is recommended
- **TREATMENTS**—gluten-free diet lifelong. Steroids, if symptoms persist despite gluten-free diet, and consider workup for enteropathy-associated lymphoma

Malabsorption Syndromes

DIFFERENTIAL DIAGNOSIS

SALIVARY (lipase, amylase; rare cause)—radiation, sicca
STOMACH (intrinsic factor, R factor; rare cause)—pernicious anemia, gastrectomy, vagotomy
HEPATOBILIARY (bile acids; 10% of extracolonic cases)—hepatic failure, cholestasis, biliary obstruction, terminal ileal resection
PANCREAS (lipase, amylase, HCO_3; 90% of extra-colonic causes)—cancer, chronic pancreatitis, cystic fibrosis
SMALL INTESTINE (brush border/enterocytes)—celiac disease, lymphoma, infectious colitis, inflammatory colitis, ischemic colitis, radiation colitis
OTHERS—β-lipoprotein (abetalipoproteinemia), lymphatics (lymphoma)

PATHOPHYSIOLOGY

COMPLICATIONS OF MALNOURISHMENT—infections (sepsis, abscess, pneumonia), poor wound healing, respiratory failure, death

CLINICAL FEATURES

HISTORY—diarrhea (watery, steatorrhea), flatus, abdominal distension, abdominal pain (suggests chronic pancreatitis, Crohn's disease, or pseudo-obstruction as otherwise uncommon in malabsorption), N&V, symptoms in relation to meals (may occur within 90 min of carbohydrate ingestion), anorexia, weight loss, diet, past medical history (type 1 diabetes, celiac disease, IBD, recurrent peptic ulcer disease, previous surgery, psychiatric disorders, alcohol), medications (laxatives, diuretics, illicit drugs)

Related Topics
Cachexia (p. 449)
Celiac Disease (p. 139)
Vitamin B12 Deficiency (p. 459)

RATIONAL CLINICAL EXAMINATION SERIES: IS THIS PATIENT MALNOURISHED?
HISTORY—**weight change** (overall loss in past 6 months, change in past 2 weeks), **dietary intake change** relative to normal (duration, types include suboptimal solid diet, hypocaloric liquids, full liquid diet, starvation), **gastrointestinal symptoms** >**2 weeks** (nausea, vomiting, diarrhea, anorexia), **functional capacity** (duration, working suboptimally, ambulatory, bedridden)
PHYSICAL—**loss of subcutaneous fat** (triceps, chest), **muscle wasting** (quadriceps, deltoids), **swelling** (ankle edema, sacral edema, ascites)

RISK OF MAJOR POSTOPERATIVE COMPLICATIONS BASED ON SUBJECTIVE GLOBAL ASSESSMENT (SGA)

	LR+
Well nourished	
Defined as <5% weight loss or >5% total weight loss but recent gain and improvement in appetite	0.66
Moderately malnourished	
Defined as 5–10% weight loss without recent stabilization or gain, poor dietary intake, and mild (1+) loss of subcutaneous tissue	0.96
Severely malnourished	
Defined as ongoing weight loss of >10% with severe subcutaneous tissue loss and muscle wasting often with edema	4.44

APPROACH—"SGA is an accurate predictor of patients who are at higher risk of developing complications such as infection or poor wound healing"

JAMA 1994 271:1

UPDATE—several markers have been compared to the SGA for predicting malnutrition. Serum albumin <3.0 g/dL increases likelihood of moderate/severe malnutrition (LR + 3.3), but is not specific. A positive simplified Malnutrition Screening Tool (have you lost weight without trying, how much weight have you lost [kg], and have you been eating poorly because of decreased appetite) increases likelihood of malnutrition (LR+ 13)

The Rational Clinical Examination. McGraw-Hill, 2009

INVESTIGATIONS

BASIC

- LABS—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, PTT, fasting lipid profile, Ca, Mg, PO_4, albumin, pre-albumin,

INVESTIGATIONS (CONT'D)

carotene, Fe, ferritin, antitransglutaminase antibody, vitamin B12, RBC folate
- **IMAGING**—US abd

SPECIAL
- **COLONOSCOPY**—for Crohn's
- **GASTROSCOPY**—for Celiac disease
- **MRCP/ENDOSCOPIC US**—if suspect chronic pancreatitis
- **STOOL FAT**— > 6 g/day suggests steatorrhea
- **D-XYLOSE TEST**—if suspect malabsorption
- **BREATH TEST**—for carbohydrate malabsorption, small bowel bacterial overgrowth and lactose intolerance, including H_2, $^{14}CO_2$, or $^{13}CO_2$
- **ANTIINTRINSIC FACTOR ANTIBODY**—for vitamin B12 deficiency (has replaced historical Schilling test)

MANAGEMENT

SYMPTOM CONTROL—dietician consult. Consider supplemental nutrition

TREAT UNDERLYING CAUSE

SPECIFIC ENTITIES

MARASMUS SYNDROME—deficiency of calories resulting in stunted growth in children, loss of body fat, and generalized wasting of lean body mass without significant edema

SPECIFIC ENTITIES (CONT'D)

KWASHIORKOR SYNDROME—deficiency of protein with preserved adipose tissue but significant edema, muscle atrophy, and amenorrhea

FAT-SOLUBLE VITAMIN DEFICIENCY ★KADE★
- **VITAMIN K DEFICIENCY**—increased bleeding tendencies
- **VITAMIN A DEFICIENCY**—follicular hyperkeratosis, night blindness
- **VITAMIN D DEFICIENCY**—paresthesia, tetany, weakness, fractures due to osteomalacia
- **VITAMIN E DEFICIENCY**—skeletal myopathy, spinocerebellar ataxia, pigmented retinopathy, and hemolysis

WATER-SOLUBLE VITAMIN DEFICIENCY
- **VITAMIN B1 (THIAMINE) DEFICIENCY**—Wernicke syndrome, Korsakoff syndrome, Leigh's syndrome (subacute necrotizing encephalomyopathy)
- **VITAMIN B3 (NIACIN, NICOTINIC ACID) DEFICIENCY ★DDDD★**—**D**ermatitis (photosensitive, pigmented, pellagra), **D**iarrhea, **D**ementia, **D**eath
- **VITAMIN B6 (PYRIDOXINE) DEFICIENCY**—cheilosis, painless glossitis, acrodermatitis, angular stomatitis
- **VITAMIN C DEFICIENCY**—scurvy with impaired collagen synthesis leading to ecchymoses, gum bleeding, petechiae, hyperkeratosis, impaired wound healing, arthralgia, weakness, neuropathy, and depression

Constipation NEJM 2003 349:14

DIFFERENTIAL DIAGNOSIS

★DUODENUM★

DIET—low fiber, dehydration

ΨSYCHIATRY—depression, somatization, obsessive compulsive disorder

OBSTRUCTION—cancer, strictures, adhesions

DRUGS—opioids, TCAs, neuroleptics, antihistamines, calcium channel blockers, iron, antacids

ENDOCRINE—diabetes, hypothyroidism, hypercalcemia, hypokalemia, hypomagnesemia, uremia

NEUROLOGIC—spinal cord compression/injury, Parkinson's, multiple sclerosis, stroke, autonomic neuropathy (cachexia–anorexia syndrome)

UNKNOWN

MISCELLANEOUS—irritable bowel syndrome (IBS), amyloidosis, scleroderma, immobility

INVESTIGATIONS

BASIC
- **LABS**—CBCD, lytes, urea, Cr, glucose, TSH, Ca, Mg
- **IMAGING**—AXR

DIAGNOSTIC ISSUES

CONSTIPATION SCORE—based on flat abdominal X-ray. Divide into four quadrants (ascending, transverse, descending, and rectosigmoid colon). Rate amount of stool in each quadrant from 0–3. A total score >6/12 suggests constipation

MANAGEMENT

LIFESTYLE CHANGES—wheat **bran**, high-bran cereals, ***psyllium/Metamucil*** 2–3 teaspoon/day, **exercise**, **hydration** (8–10 glasses/day)

SYMPTOM CONTROL—**laxatives** (in order of increasing potency: *docusate* 100–240 mg PO

MANAGEMENT (CONT'D)

daily-QID, *senna* 1–4 tabs PO daily-QID, *milk of magnesia* 15–30 mL PO BID, *sorbitol* 15–30 mL PO daily-BID, *lactulose* 15–60 mL PO daily, *magnesium citrate* 150–300 mL PO daily, *bisacodyl/dulcolax suppositories* 1 PR PRN, *tap water enema* 500 mL PR PRN, *mineral oil enema* 100–250 mL PR PRN, *polyethylene glycol electrolyte solution [PEG]* 250–4000 mL PO PRN). **Manual disimpaction**. For patients with spinal cord injury, it is important to use rectal measures (enemas, suppositories) as significant diarrhea/leakage could occur with oral medications alone

TREAT UNDERLYING CAUSE—stop potentially constipation-causing medications if possible

SPECIFIC ENTITIES

IRRITABLE BOWEL SYNDROME (IBS)

- **PATHOPHYSIOLOGY**—heightened response to noxious visceral stimuli, such as balloon distention of the rectum and sigmoid colon
- **CLINICAL FEATURES**—Rome criteria define IBS as >3 months of abdominal pain relieved with defecation, associated with a change in the frequency or consistency of stool, plus two of the following for >25% of days: disturbed defecation (>3 bowel movements/day or <3 bowel movements/week), altered stool formation, altered stool passage (straining, urgency, or feeling of incomplete evacuation), passage of mucus, bloating, or feeling of abdominal distention

SPECIFIC ENTITIES (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES: WILL THE HISTORY AND PHYSICAL EXAMINATION HELP ESTABLISH THAT IRRITABLE BOWEL SYNDROME IS CAUSING THIS PATIENT'S LOWER GASTROINTESTINAL TRACT SYMPTOMS?

MANNING CRITERIA—abdominal pain relieved by defecation, more frequent stools with onset of pain, looser stools with onset of pain, passage of mucus per rectum, feeling of incomplete emptying, patientreported visible abdominal distension

ROME I CRITERIA—abdominal pain or discomfort relieved with defecation or associated with a change in stool frequency or consistency for ≥3 months, plus ≥2 of the following on at least 25% of occasions or days: (1) altered stool frequency, (2) altered stool form, (3) altered stool passage, (4) passage of mucus per rectum, (5) bloating or distension

KRUIS MODEL—a computer model based on a number of symptoms and signs. Symptoms include (1) abdominal pain, flatulence, or bowel irregularity for >2 years; (2) description of abdominal pain as "burning, cutting, very strong, terrible, feeling of pressure, dull, boring, or not so bad"; and (3) alternating constipation and diarrhea. Signs include (1) abnormal physical findings and/or history pathognomonic for any diagnosis other than IBS, (2) ESR >10 mm/h, (3) leukocytosis $>10\times10^9$/L, (4) hemoglobin <120 g/L [<12 g/dL] for females or <140 g/L [<14 g/dL] for males, (5) impression by the physician that the patient's history suggests blood in the stool

	Sens	Spc	LR+	LR–
Symptoms				
Lower abd pain	90%	32%	1.3	0.29
Passage of mucus	45%	65%	1.2	0.88
Feeling of incomplete evacuation	74%	45%	1.3	0.62
Looser stools at onset of pain	59%	73%	2.1	0.59
More frequent stools at onset of pain	53%	72%	1.9	0.67
Pain relieved by defecation	60%	66%	1.8	0.62
Patient reported visible abdominal distension	39%	77%	1.7	0.79
Diagnostic criteria				
Manning criteria	78%	72%	2.9	0.29
Rome I criteria	71%	85%	4.8	0.34
Kruis system	77%	89%	8.6	0.26

APPROACH—"absence of abdominal pain reduced the likelihood of IBS. Overall, individual symptoms have limited accuracy for diagnosing IBS in patients referred with lower GI symptoms. The accuracy of the Manning criteria, Rome I criteria and Kruis scoring system were only modest"

JAMA 2008 300:15

Related Topics
Acute Abdominal Pain (p. 128)
Constipation in the Palliative Setting (p. 448)
Nausea and Vomiting (p. 123)
Opioid Use (p. 443)

SPECIFIC ENTITIES (CONT'D)

- **ASSOCIATIONS**—patients with IBS are more likely to have functional dyspepsia, urinary symptoms, dysmenorrhea, dyspareunia, sexual dysfunction, proctalgia fugax, a history of physical or sexual abuse, and fibromyalgia
- **DIAGNOSIS**—IBS is a diagnosis of exclusion. Consider flexible sigmoidoscopy/colonoscopy, evaluation for celiac sprue (p. 139), and stool cultures to rule out other diseases

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—reassurance, stress reduction, fiber supplementation. For constipation-prone IBS, consider osmotic laxatives (first-line), and *linaclotide* 290 μg PO daily (for persistent constipation). For diarrhea-prone IBS, consider *loperamide* 2–4 mg PO daily (first-line), and *alosetron* 0.5–1 mg PO BID × 12 weeks (for ♀ with severe diarrhea; 5HT3 antagonist). For abdominal pain, consider antispasmodics (*hyoscyamine* 0.125–0.25 mg PO q4–6 h PRN), TCAs (*amitriptyline* 10–75 mg qhs), *desipramine* 25–150 mg PO daily, and SSRIs for abdominal pain. Cognitive behavioral therapy may also be useful

NEJM 2008 358:16

Acute Liver Failure

DIFFERENTIAL DIAGNOSIS

HEPATOCELLULAR INJURY PATTERN (↑↑ AST/ALT ± ↑ ALP/bili)

- **INFECTIOUS**—HAV, HBV, HCV (rare), HDV, HEV, EBV, CMV, HSV, VZV, schistosomiasis, toxoplasmosis, bacterial cholangitis
- **FATTY LIVER**—alcoholic, non-alcoholic steatohepatitis (NASH)
- **TOXIC**—acetaminophen, NSAIDs, amiodarone, labetalol, statins, phenytoin, valproic acid, fluoroquinolones, amoxicillin/clavulanate, sulfonamides, tetracyclines, isoniazid, azoles, halothane, glyburide, propylthiouracil, Amanita phalloides mushroom, heavy metals, anabolic steroids, cocaine, ecstasy, phencyclidine
- **VASCULAR**—ischemic ("shock liver"), Budd–Chiari, congestive, venoocclusive disease (BMT, chemotherapy, OCP)
- **NEOPLASTIC**—hepatoma
- **AUTOIMMUNE**—autoimmune hepatitis
- **HEREDITARY**—Wilson's, hemochromatosis, α1-antitrypsin deficiency, glycogen storage disease
- **PREGNANCY**—acute fatty liver of pregnancy, HELLP
- **OTHERS**—liver surgery, Reye's syndrome with viral illness, and ASA use
- **NON-HEPATIC**—celiac sprue, adrenal insufficiency, myopathy, strenuous exercise

CHOLESTATIC PATTERN (↑↑ ALP/bilirubin ± ↑ AST/ALT)

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **BACTERIAL CHOLANGITIS**
- **BILIARY EPITHELIAL DAMAGE**—hepatitis, cirrhosis, biliary colic
- **INTRAHEPATIC CHOLESTASIS**—sepsis, drugs (amoxicillin–clavulanate, erythromycin, trimethoprim–sulfamethoxazole, indinavir, nevirapine, allopurinol, carbamazepine, captopril, chlorpromazine, diltiazem, estrogens, fluphenazine, gold, imipramine), TPN, primary biliary cirrhosis
- **BILIARY DUCTAL OBSTRUCTION**—choledocholithiasis, pancreatic cancer, cholangiocarcinoma, pancreatitis, primary sclerosing cholangitis

INFILTRATIVE PATTERN (↑↑ ALP with ↑ GGT ± ↑ bili/AST/ALT)

- **INFECTIOUS**—TB, histoplasmosis, abscess (bacterial, amoebic)
- **NEOPLASM**—hepatoma, lymphoma
- **GRANULOMATOUS DISEASE**—sarcoidosis, TB, fungal
- **OTHERS**—amyloidosis

ISOLATED HYPERBILIRUBINEMIA (↑↑ bilirubin only)—see JAUNDICE (p. 155)

PATHOPHYSIOLOGY

DEFINITIONS

- **ABNORMAL LIVER ENZYMES**—defined as ±2 standard deviations, so 5% of the population would have abnormal liver enzymes by definition

PATHOPHYSIOLOGY (CONT'D)

- **ACUTE (FULMINANT) LIVER FAILURE**—development of jaundice, coagulopathy, and encephalopathy within 8 weeks of onset of hepatocellular injury; subclassified into hyperacute (day 0–7), acute (day 8–28) and subacute (day >28)
- **CHRONIC HEPATITIS**—↑ ALT >6 months

Related Topics
Acetaminophen Overdose (p. 115)
Alcohol-Related Issues (p. 117)
Hemochromatosis (p. 482)
Hepatitis B (p. 145)
Hepatitis C (p. 147)
Hepatoma (p. 227)
Liver Diseases in Pregnancy (p. 471)
Wilson's Disease (p. 150)

LIVER ENZYMES BY CATEGORY

- **SYNTHETIC FUNCTION**—INR (dependent on factors I, II, V, VII, IX, X), bilirubin (heme breakdown product), albumin (synthesis), fibrinogen
- **HEPATIC INJURY**—AST (intracellular; liver, heart, skeletal, kidneys, brain, pancreas, lungs, RBC, WBC), A**L**T (intracellular; specific for **L**iver), ALP (liver, gut, bone, placenta), GGT, 5'NT, LDH (bone, muscle, liver, lungs)

COMPLICATIONS OF HEPATIC FAILURE

★SCREAM★

- **S**epsis
- **C**oagulopathy
- **R**enal failure
- **E**ncephalopathy
- **A**scites
- **M**etabolic changes (hypoglycemia, electrolyte abnormalities, acidosis)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, albumin, HAV IgM, HAV IgG, HBsAg, HBsAb, HBcIgM, HBcIgG, lactate
- **IMAGING**—US abd (with Doppler), CT abd

SPECIAL

- **LABS**—EBV, CMV, HSV, ANA, anti-smooth muscle antibody (ASMA), anti-mitochondrial antibody (AMA), quantitative immunoglobulin, ferritin, Fe, TIBC, % sat, ceruloplasmin, α1-antitrypsin, AFP, antitransglutaminase antibody, lipase, amylase, LDH, haptoglobin, acetaminophen, CK, TSH
- **ERCP/MRCP**
- **GASTROSCOPY**
- **LIVER BIOPSY**

DIAGNOSTIC AND PROGNOSTIC ISSUES

↑ **AST/SGOT**—do panel of liver function tests. If isolated rise, consider non-hepatic causes. Otherwise, same as ALT workup. AST > ALT suggests alcoholic liver disease, fatty liver, or cirrhosis

↑ **ALT/SGPT**—if symptomatic and presence of risk factors for liver disease, liver dysfunction (↓ albumin, ↑ INR, ↑ bili), ↑ ALT or AST >3× upper limit of normal, or ↑ ALT >6 months, consider basic workup including abdominal US with Doppler, viral serologies, ANA, ASMA, quantitative Ig, ceruloplasmin, iron studies, antitransglutaminase antibody, and possibly liver biopsy

↑ **ALP/BILI**—ask about pain, symptoms of infiltrative disease, or IBD. To confirm liver involvement, perform bilirubin fractionation, GGT, 5'NT, abdominal US, AMA, and quantitative Ig. Consider MRCP/ERCP/EUS and liver biopsy

MONITORING—INR and bilirubin are much more useful to monitor liver function compared to transaminases

SURVIVAL IN ACUTE HEPATIC FAILURE—35% in hyperacute, 7% in acute, and 14% subacute

MANAGEMENT

SYMPTOM CONTROL

- **ACUTE**—ABC, O_2, IV hydration
- **ELEVATED INTRACRANIAL PRESSURE**—for cerebral edema, consider prophylactic phenytoin, raise head of bed, hyperventilate, dexamethasone, mannitol, avoid excessive fluids
- **SEPSIS**—antibiotics
- **COAGULOPATHY**—*vitamin K* 10 mg IV/PO, FFP 2–4 U IV (only if active bleeding or invasive procedures, or difficult to follow INR afterward)
- **ACUTE RENAL FAILURE**—supportive renal replacement. Consider midodrine, octreotide, and albumin
- **ENCEPHALOPATHY**—limit protein intake up to 1 g/kg/day. *Lactulose* 30 g PO QID PRN titrate to 2–4 bowel movements/day; if patient obtunded and NPO, consider lactulose 300 mL (mixed with 700 mL of H_2O or NS) PR via rectal balloon catheter QID until awake

MANAGEMENT (CONT'D)

- **ACIDOSIS**—3 amp $NaHCO_3$ diluted in 1000 mL D5W (i.e. 150 mmol/L of HCO_3^-) as continuous IV infusion at 150–250 mL/h. Give with caution as risk of cerebral edema with increased fluid
  - **HYPOGLYCEMIA**—D10W, tube feed, TPN
  - **DETOXIFICATION**—*N-acetylcysteine* 150 mg/kg IV (~60 mL) in 200 mL D5W over 1 h, then 50 mg/kg (~20 mL) in 500 mL D5W over 4 h, then 100 mg/kg (~40 mL) in 1 L D5W over 16 h. Alternatively, *N-acetylcysteine* 140 mg/kg PO/NG, followed by 70 mg/kg q4h for 17 doses. May continue *N*-acetylcysteine until INR normalized

PREVENTION—**hepatitis B vaccine** (0, 1, 6 months), **HBIG** (post-exposure), hepatitis A vaccine (see p. 305)

TREAT UNDERLYING CAUSE—**hepatitis B** (if acute liver failure from HBV, provide supportive care only without active HBV treatment). **Hepatitis C** (pegylated interferon ± ribavirin). **Alcoholic hepatitis** (abstinence, nutrition, *prednisolone* 40 mg PO × 28 days but avoid if pancreatitis, GI bleed, renal failure, or active infection; *pentoxifylline* 400 mg PO TID × 28 days [expect ↓ bilirubin on day 7 vs. day 1. A lack of response suggests limited survival benefit]). **Autoimmune hepatitis** (steroids). **Wilson's disease** (D-penicillamine, trientine)

LIVER TRANSPLANT—patients with fulminant liver failure should be transferred to acute care centers with liver transplant expertise

TREATMENT ISSUES

LIVER TRANSPLANT

- **ALLOCATION**—based on ABO blood type, body size, wait designation, and degree of urgency
- **KING'S COLLEGE CRITERIA FOR TYLENOL OVERDOSE ACUTE HEPATIC FAILURE** (rule of **3**'s)—either arterial pH <**7.3** or grade **III** or IV encephalopathy, plus Cr >**300** μmol/L [>**3.3** mg/dL], plus INR >**6.5** (or PT >100 s)
- **KING'S COLLEGE CRITERIA FOR NON-TYLENOL ACUTE HEPATIC FAILURE**—INR >3 or any 3 of following: age <10 or >40, non-A non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions, duration of jaundice before onset of encephalopathy >7 days, INR >1.5, bilirubin >308 μmol/L [179 mg/dL]
- **CONTRAINDICATIONS**—malignancy (except hepatocellular carcinoma), irreversible cardiopulmonary comorbidities, neuropsychiatric comorbidities, sepsis, substance abuse, noncompliance, HIV

SPECIFIC ENTITIES

AST/ALT THOUSAND CLUB—viral hepatitis, ischemic liver (hypotension, hypoxia, sepsis), drugs/toxins (acetaminophen/paracetamol), autoimmune hepatitis, gallstone disease (acute bile duct obstruction), acute Budd–Chiari syndrome, hepatic artery ligation

ALCOHOLIC LIVER DISEASE

- **SUBTYPES**—fatty liver, alcoholic hepatitis, micronodular cirrhosis
- **DIAGNOSIS**—AST:ALT = 2:1 (low ALT activity due to alcohol-related pyridoxal 5-phosphate deficiency), rare for AST to be >8× normal and for ALT to be >5× normal. GGT ↑, ALP ↑, bilirubin ↑
- **TREATMENTS**—abstinence, nutrition, *prednisolone* 40 mg PO × 28 days, *pentoxifylline* 400 mg PO TID × 4 weeks

NON-ALCOHOLIC STEATOHEPATITIS (NASH)

- **ASSOCIATIONS**—obesity, hyperlipidemia, diabetes, Cushing's, TPN, high-protein diets for weight loss, amiodarone, tamoxifen
- **DIAGNOSIS**—liver biopsy
- **TREATMENTS**—weight loss (diet, exercise), omega 3-6-9 fatty acids, metformin for diabetes, statins for dyslipidemia

Hepatitis B

NEJM 2004 350:11; NEJM 2008 359:14

PATHOPHYSIOLOGY

NATURAL HISTORY—acute hepatitis → chronic disease develops in >90% of neonates, in 10% if 12 years old, and in <1% if >12 years old → 12–20% with chronic hepatitis progress to cirrhosis in 5 years → 20% with compensated cirrhosis progress to decompensation in 5 years and 6–15% with compensated cirrhosis progress

PATHOPHYSIOLOGY (CONT'D)

to hepatocellular carcinoma. Lifetime risk of hepatocellular carcinoma/death in patients with chronic hepatitis is 40% for ♂ and 15% for ♀

ACUTE HEPATITIS B—may range from subclinical/anicteric hepatitis (70%) to icteric hepatitis (30%) and even fulminant hepatic failure (0.5–1%). Symptoms may include fever, anorexia, rash,

PATHOPHYSIOLOGY (CONT'D)

nausea, jaundice, RUQ tenderness, arthralgia, and arthritis. ↑↑ ALT and AST

CHRONIC HEPATITIS B

- **REPLICATIVE PHASE WITH IMMUNE TOLERANCE** (only if vertical transmission)—HBeAg positive, asymptomatic as lack of immune response in children. May last 10–30 years
- **REPLICATIVE PHASE WITH IMMUNE CLEARANCE**—HBeAg positive with seroconversion to HBeAb, may be symptomatic with increased liver enzymes due to immune response against HBV
- **NON-REPLICATIVE PHASE**—HBeAb positive, low level of viral replication. Usually normal liver enzymes
- **SUSPECT PROGRESSION TO CIRRHOSIS**—if hypersplenism or impaired synthetic function (↑ INR, ↑ bilirubin, hypoalbuminemia)

GENOTYPES—there are currently eight different genotypes (A to H)

RISK FACTORS—vertical transmission, endemic areas, transfusions, dialysis, healthcare workers, IDU, high-risk sex/homosexuals, body piercing, tattoos, organ transplantation

Related Topics
Acute Liver Failure (p. 143)
Chronic Liver Failure (p. 149)
HBV/HIV Co-infection (p. 291)
Hepatitis C (p. 147)
Hepatoma (p. 227)

CLINICAL FEATURES

HISTORY—symptoms of liver failure (jaundice, bleeding, infections, ascites, confusion), weight change, risk factors of hepatitis (family history, sexual activity, IDU, tattoos, piercing, healthcare worker, transfusions, dialysis), past medical history (alcohol, HCV, HIV), medication history

PHYSICAL—liver examination, stigmata of chronic liver disease (see p. 149), weight

EXTRAHEPATIC MANIFESTATIONS OF HBV—polyarteritis nodosa, membranous nephropathy, membranoproliferative glomerulonephritis

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, albumin, HBV serology (HBsAb, HBsAg, HBcIgM, HBcIgG to determine infection/immune status, HBeAg, HBeAb, HBV DNA to see if active replication), HAV serology, HCV serology, HDV serology, iron, TIBC, HIV serology
- **IMAGING**—US abd

SPECIAL

- **LIVER BIOPSY**
- **FIBROSCAN**—non-invasive assessment of liver fibrosis using ultrasound

DIAGNOSTIC ISSUES

HEPATITIS B SEROLOGY

- **HBsAg**—hepatitis B surface antigen. Positive if active infection
- **HBcIgM**—IgM antibody against hepatitis B core antigen. Suggestive of early infection (indicates the window period) or reactivation
- **HBsAb**—antibody against hepatitis B surface antigen. Positive if immunized (through past infection or vaccination)
- **HBcIgG**—IgG antibody against hepatitis B core antigen. Suggestive of hepatitis B exposure
- **HBeAg**—hepatitis B envelope protein. HBeAg positivity suggests high viral replication with high infectivity. However, HBeAg negativity without HBeAb positivity suggests chronic HBV infection with pre-core mutants/promoter mutations, with a more aggressive phenotype than HBeAg + HBV, more treatment failures, and progressive hepatic injury. HBeAg negative infection is associated with fluctuating ALT and lower levels of HBV DNA. By definition, HBeAg seroconversion cannot occur
- **HBeAb**—antibody against hepatitis B envelope protein. Suggests low/no viral replication, usually with low infectivity
- **HBV DNA**—direct determination of hepatitis B virus DNA. HBV DNA level reflects viral replication activity and is associated with the risk of cirrhosis and hepatoma. HBV DNA determination is important in both HBeAg+ and HBeAg– individuals to determine need for antiviral therapy

DIAGNOSTIC ISSUES (CONT'D)

	HBsAg	HBcIgM	HBsAb	HBcIgG	HBeAg	HBeAb
Acute infection						
Early	+	–	–	–	+	–
Window	–	+	–	–	+	–
Late	–	+/–	+	–	+	–
Immunity						
Vaccinated	–	–	+	–	–	–
Cured	–	–	+/–	+	–	+
Chronic infection						
Infectious/active	+	–	–	+	+	–
Pre-core mutant	+	–	–	+	–	–
Low replicative	+	–	–	+	–	+

MANAGEMENT

LIFESTYLE CHANGES—avoid alcohol use, sexual education, HBV vaccination

TREAT UNDERLYING CAUSE—interferon, pegylated interferon, lamivudine, adefovir, entecavir, telbivudine, tenofovir

VACCINATION—household and sexual contacts

TREATMENT ISSUES

TREATMENT DECISION FOR CHRONIC HEPATITIS B INFECTIONS

- **HBeAg positive patients**—consider treatment if HBV DNA level >20,000 IU/mL and elevated ALT >1× upper limit of normal for 3–6 months; or significant inflammation and fibrosis on biopsy, FibroScan, Fibrotest, or US abd regardless of HBV DNA or ALT levels
- **HBeAg negative patients (pre-core or core promoter mutations)**—consider treatment if HBV DNA >2000 IU/mL and elevated ALT >1× upper limit of normal for 3–6 months; or significant inflammation and fibrosis on biopsy, FibroScan, Fibrotest, or US abd regardless of HBV DNA or ALT levels

Please see **Can J Gastroenterol 2012 21:12** at www.hepatology.ca for consensus statement on management of hepatitis B

Hepatitis C NEJM 2001 345:1

PATHOPHYSIOLOGY

NATURAL HISTORY—acute infection → 55–85% of total will develop chronic infection → 50% of total will develop chronic hepatitis → 5–20% of total will develop cirrhosis → 3–5%/year of acute decompensation, also 1–5%/year of developing hepatocellular carcinoma (after 10–30 years)

RISK FACTORS FOR TRANSMISSION

- **high**—IDU, transfusions, immigration from endemic regions
- **low**—perinatal transmission, transfusion before 1992, body piercing, long-term dialysis, occupational exposure, intranasal drug use, multiple sexual partners

CLINICAL FEATURES

HISTORY—symptoms of liver failure (jaundice, bleeding, infections, ascites, confusion), weight change, risk factors of hepatitis (sexual activity, IDU, tattoos, piercing, healthcare worker, transfusions, dialysis), past medical history (alcohol, HBV, HIV), medication history

PHYSICAL—liver examination, stigmata of chronic liver disease, weight. Also examine for extrahepatic manifestations of HCV

Related Topics
Acute Liver Failure (p. 143)
Chronic Liver Failure (p. 149)
HCV/HIV Co-infection (p. 291)
Hepatitis B (p. 145)
Hepatoma (p. 227)

EXTRAHEPATIC MANIFESTATIONS OF HCV

- **HEENT**—uveitis, corneal ulcer, sialadenitis
- **RENAL**—nephritic syndrome (MPGN II), nephrotic syndrome (membranous)

CLINICAL FEATURES (CONT'D)

- **HEMATOLOGIC**—aplastic anemia, lymphoma, cryoglobulinemia, ITP
- **VASCULAR**—necrotizing vasculitis, polyarteritis nodosa
- **RHEUMATOLOGIC**—arthralgias, arthritis, myalgia, sicca
- **NEUROLOGIC**—weakness, peripheral neuropathy
- **ENDOCRINE**—diabetes, antithyroid antibodies
- **DERMATOLOGIC**—psoriasis (20%), pruritus, Raynaud's, porphyria cutaneous tarda, lichen planus, cutaneous necrotizing vasculitis

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, albumin, anti-HCV IgM and total (sens 92–97%), HCV RNA PCR (qualitative, quantitative), genotyping, βhCG (before treatment), HAV serology, HBV serology, HDV serology, iron, TIBC, HIV serology
- **IMAGING**—US abd

SPECIAL

- **LIVER BIOPSY**—not mandatory before starting treatments
- **FIBROSCAN**—non-invasive assessment of liver fibrosis using ultrasound

PROGNOSTIC ISSUES

GOOD PROGNOSTIC FACTORS—age <40, female, weight <75 kg [165 lbs], low titer, genotype 2/3, mild fibrosis

POOR PROGNOSTIC FACTORS—age of infection ≥40, male, high BMI, alcoholism, HIV co-infection

UNCERTAIN PROGNOSTIC FACTORS—genotype, viral load, route of transmission

MANAGEMENT

TREAT UNDERLYING CAUSE (Note: the treatment paradigm is rapidly evolving. The regimens below are based on AASLD guidelines, and have a response rate of over 90%)

- **GENOTYPE 1 OR 4**—daily fixed-dose combination of ledipasvir/sofosbuvir for 12 weeks; OR paritaprevir/ritonavir/ombitasvir plus dasabuvir and weight-based ribavirin for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis); OR sofosbuvir plus simeprevir with or without ribavirin for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis)

MANAGEMENT (CONT'D)

- **GENOTYPES 2**—sofosbuvir plus ribavirin for 12 weeks; treatment to 16 weeks is recommended in patients with cirrhosis
- **GENOTYPES 3**—sofosbuvir plus ribavirin for 24 weeks
- **GENOTYPE 4 (alternative regimens)**—daily sofosbuvir and ribavirin plus weekly pegylated interferon for 12 weeks; OR daily sofosbuvir plus simeprevir with or without weight-based ribavirin for 12 weeks

ORTHOTOPIC LIVER TRANSPLANT

TREATMENT ISSUES

TREATMENT DECISION—complex decision depending on patient's wishes, risk of progression, chance of response (genotypes 2 and 3 better), and any contraindications to treatment

- **GOOD CANDIDATES**—chronic hepatitis with significant fibrosis, compensated cirrhosis, stable CBC and Cr, good adherence. Elevated ALT is no longer considered a decision factor
- **SPECIAL CIRCUMSTANCES** (regimen modification required and should be done under expert guidance)—acute HCV, HIV/HCV, HBV/HCV previous treatment failures, liver transplant, renal failure, current drug or alcohol use
- **ABSOLUTE CONTRAINDICATION**—decompensated cirrhosis

Please see **Can J Gastroenterol 2012 26:6** at www.hepatology.ca for consensus statement on management of hepatitis C

NOVEL THERAPEUTICS

- **NS3/4A PROTEASE INHIBITORS**—boceprevir (Victrelis), telaprevir (Incivek), and simeprevir (Olysio). The NS3/4A protease is essential for cleaving and processing the HCV-encoded polyprotein
- **NS5B POLYMERASE INHIBITOR**—sofosbuvir (Sovaldi). NS5B is necessary for HCV RNA replication
- **NS5A PHOSPHOPROTEIN INHIBITOR**—ledipasvir (Harvoni in combination with sofosbuvir). NS5A is important for HCV RNA replication, assembly and secretion

MONITORING DURING HCV THERAPY—CBC weekly for 4 weeks, then CBC, AST, ALT, uric acid monthly, TSH and ANA every 3 months, and HCV RNA at 4, 12, and 24 weeks during treatment and 6 months after therapy. For significant anemia and neutropenia, give EPO and GCSF, respectively. Also monitor for depression

Chronic Liver Disease: Cirrhosis

DIFFERENTIAL DIAGNOSIS

INFECTIONS—HBV, HCV, HDV, schistosomiasis, toxoplasmosis
STEATOHEPATITIS—alcohol, non-alcoholic steatohepatitis (NASH)
MEDICATIONS—acetaminophen/paracetamol (chronic use, controversial)
AUTOIMMUNE—autoimmune hepatitis
NEOPLASM—hepatoma, cholangiocarcinoma

DIFFERENTIAL DIAGNOSIS (CONT'D)

METABOLIC—hemochromatosis, Wilson's, α1-antitrypsin deficiency, glycogen storage disease
BILIARY CIRRHOSIS—primary biliary cirrhosis, primary sclerosing cholangitis, secondary biliary cirrhosis (stones, strictures)
CARDIAC CIRRHOSIS—chronic right-sided heart failure

PATHOPHYSIOLOGY

CHILD–PUGH CLASSIFICATION OF LIVER CIRRHOSIS

Points	Encephalopathy	Ascites	Albumin	Total bili	INR
1	0	None	>35 g/L [>3.5 g/dL]	<34 μM [<2 mg/dL]	<1.7
2	1–2	Slight	28–35 g/L [2.8–3.5 g/dL]	34–51 μM [2–3 mg/dL]	1.7–2.3
3	3–4	Mod	<28 g/L [<2.8 g/dL]	>51 μM [>3 mg/dL]	>2.3

PATHOPHYSIOLOGY (CONT'D)

The Child–Pugh score is calculated as either encephalopathy plus ascites plus INR, or albumin plus bilirubin plus INR. Patients with score >7 or any clinical signs of decompensation (variceal bleeding, ascites, encephalopathy) should be considered for liver transplantation. Alternative calculation is a total score of all five parameters, grade A = 5–6, grade B = 7–9, grade C = 10–15

MODEL FOR END-STAGE LIVER DISEASE (MELD) SCORE—originally designed to predict survival in patients with portal hypertension undergoing elective TIPS procedure, now used as a tool for organ allocation in patients with chronic liver disease. The MELD score ranges from 6 to 40, with higher values indicating a worse prognosis

- **ORIGINAL MELD** = $9.57 \times \log_e$(Cr in mg/dL) + $3.78 \times \log_e$(total bilirubin in mg/dL) + $11.2 \times \log_e$(INR) + 6.43
- **UNITED NETWORK OF ORGAN SHARING MELD (UNOS-MELD)** = same formula but fixed lower limit of 1 for all variables and fixed upper limit of 4 mg/dL for Cr. Furthermore, Cr set at 4 for patients on renal replacement therapy
- **MELD-Na** = UNOS-MELD − Na − [0.025 × MELD × (140 − Na)] + 140

For web-based calculator, please see www.mayoclinic.org/meld/

CLINICAL FEATURES

HISTORY—symptoms of liver failure (jaundice, bleeding, infections, ascites, confusion), weight change, risk factors of hepatitis (sexual activity, IDU, tattoos, piercing, healthcare worker, transfusions, dialysis), past medical history (alcohol, hereditary disorders), medication history (acetaminophen/paracetamol, other hepatotoxins)

PHYSICAL

- **STIGMATA OF CHRONIC LIVER DISEASE**—leukonychia, Terry's nails, clubbing, Dupuytren's contractures, palmar erythema, asterixis, scleral icterus, altered mental status, parotid enlargement, fetor hepaticus, spider angiomas, gynecomastia, ascites, splenomegaly, caput medusa, hemorrhoids, testicular atrophy, proximal muscle weakness, peripheral edema, petechiae
- **CLUES TO ETIOLOGY**—obesity (fatty liver), excoriations (PBC), tattoos/needle tracks (hepatitis), bronze skin (hemochromatosis), Kayser–Fleischer rings (Wilson's disease)

DISTINGUISHING LIVER FROM RIGHT KIDNEY

1. The liver has no palpable upper border and extends more laterally and medially
2. The liver is not usually ballotable, but the kidney is because of its retroperitoneal position

CLINICAL FEATURES (CONT'D)

3. The percussion note is dull over the liver but is usually tympanic over the kidney
4. A friction rub may occasionally be heard over the liver, but never over the kidney because it is too posterior
5. The liver has a shaper edge while kidney is usually more rounded

DISTINGUISHING FEATURES BETWEEN PORTAL HYPERTENSION AND VENA CAVA OBSTRUCTION

- **PORTAL HYPERTENSION**—caput medusa veins drain away from umbilicus. Stigmata of liver disease
- **IVC OBSTRUCTION**—veins prominent in the abdomen and drain up toward the superior vena cava system. No evidence of liver disease
- **SVC OBSTRUCTION**—veins prominent in the chest and drain down toward the inferior vena cava system. No evidence of liver disease

RATIONAL CLINICAL EXAMINATION SERIES: PHYSICAL EXAMINATION OF THE LIVER

INSPECTION—bulging mass over right costal margin (low sens)

PALPATION—move fingers 2 cm [0.79 in.] up at each exhalation. Palpable liver suggests hepatomegaly (LR+ 2.0, LR 0.41)

PERCUSSION—locate upper border along midclavicular line. Locate lower border with palpation, scratch test, or percussion. Liver span >12 cm (>4.7 in.) suggests hepatomegaly. Scratch test not recommended to assess liver span

AUSCULTATION—friction rubs (tumors, infection), venous hums (portal hypertension), arterial bruit (tumors, alcohol hepatitis)

APPROACH—"if clinical suspicion low, start with palpation. If positive, percuss liver span. If negative, hepatomegaly is unlikely. If clinical suspicion is high, palpate and percuss. Overall, negative findings cannot rule out abnormal liver, and positive findings cannot rule in liver disease"

JAMA 1994 271:23
The Rational Clinical Examination. McGraw-Hill, 2009

RIEDEL'S LOBE—an extension of the right lobe of the liver down below the costal margin along the anterior axillary line. It is often mistaken for a pathological enlargement of the liver or gallbladder. It is a normal anatomical variant

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, albumin, HAV serology, HBsAg, HBsAb, HBcIgM, HBcIgG, HCV serology, quantitiative immunoglobulins
- **IMAGING**—US abd (with Doppler), CT abd

SPECIAL

- **LABS**—ANA, anti-smooth muscle antibodies (anti-actin antibodies), anti-liver-kidney-microsomal (LKM) antibody, AMA, ferritin, ceruloplasmin, α1-antitrypsin, AFP, antitransglutaminase
- **GASTROSCOPY**—to check for varices
- **LIVER BIOPSY**
- **FIBROSCAN**

MANAGEMENT

TREAT UNDERLYING CAUSE—consideration for liver transplantation

SYMPTOM CONTROL—for variceal bleed prophylaxis, consider band ligation and non-selective β-blocker if moderate/large varices or Child–Pugh B/C (*nadolol* 40–80 mg PO daily, *propranolol* 20 mg PO BID, or *carvedilol* 6.25 mg PO daily-BID) and titrate to target heart rate of 55–60/min. Perform initial screen for esophageal varices with endoscopy → repeat endoscopy in 3 years if no varices; repeat in 1–2 years if small varices; endoscopic treatment (banding/glue) if moderate/large varices. For active variceal bleed after failed endoscopic therapy, consider TIPS. See UPPER GI BLEED (p. 131), HEPATIC ENCEPHALOPATHY (p. 152), and ASCITES (p. 153) for details

HEPATOMA SCREENING—for all patients with cirrhosis, and those with HBV and hepatocellular carcinoma risk factors, repeat AFP and abdominal US every 6 months for surveillance

SPECIFIC ENTITIES

CAUSES OF HEPATOMEGALY

- **PSEUDOHEPATOMEGALY**—obstructive lung disease (emphysema), subdiaphragmatic collection
- **CONGESTIVE**—right heart failure, constrictive pericarditis, tricuspid regurgitation, IVC obstruction, hepatic vein obstruction
- **INFILTRATION**—malignancy, amyloidosis, hemochromatosis, fatty liver
- **REACTIVE**—hepatitis

WILSON'S DISEASE

- **ETIOLOGY**—copper excretion defect
- **DIAGNOSIS**—Kayser–Fleischer ring, low serum ceruloplasmin, 24-h urine for copper

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—**dietary restriction** (avoid shellfish, organs, chocolate, nuts, and mushrooms), **chelating agent** (D-penicillamine or trientine), and zinc. For severe liver failure, consider orthotopic liver transplantation

AUTOIMMUNE HEPATITIS

- **SUBTYPES**—**I** (classic, female predominance, extrahepatic disease, ANA >1/160, anti-smooth muscle antibody >1/40, ↑ IgG, steroid responsive), **II** (anti-liver-kidney-microsomal [LKM] antibody, less steroid responsive), **III** (anti-SLA)
- **DIAGNOSIS**—quantitative immunoglobulins (↑ IgG), ANA, anti-smooth muscle antibody, anti-LKM antibody, liver biopsy
- **TREATMENTS**—steroids, azathioprine, or mycophenolate mofetil. For fulminant hepatitis or cirrhosis, consider liver transplantation

HEPATIC HYDROTHORAX

- **PATHOPHYSIOLOGY**—low oncotic pressure, congenital diaphragmatic defect, ascitic fluid moves to pleural space due to pressure gradient → transudative pleural effusion → decreased lung volumes → V/Q mismatch → hypoxemia
- **DIAGNOSIS**—diagnostic paracentesis/thoracentesis. US abd to assess liver and ascites. CT chest and abd to rule out other lesions. Intraperitoneal injection of ^{99}mTc-labeled serum albumin may be helpful to confirm diagnosis
- **TREATMENTS**—O_2, salt restriction, diuretics, therapeutic paracentesis, may need thoracentesis, TIPS. Avoid chest tube if possible (high risk of SBP and hepatorenal syndrome)

HEPATOPULMONARY SYNDROME

- **PATHOPHYSIOLOGY**—portal hypertension → ↓ metabolism of vasodilating substance, or ↓ production of vasoconstricting substance → pulmonary capillary dilatation → diffusion–perfusion imbalance → hypoxemia, dyspnea on exertion and/or at rest, orthodeoxia and platypnea, cyanosis, clubbing and spider nevi
- **DIAGNOSIS**—contrast echocardiogram/bubble study (presence of microbubbles in the left atrium 3–6 cardiac cycles after intravenous injection of normal saline suggests dilated pulmonary capillaries), lung perfusion scan, pulmonary angiogram (if severe hypoxemia)
- **TREATMENTS**—O_2, liver transplant

SPECIFIC ENTITIES (CONT'D)

PORTOPULMONARY HYPERTENSION

- **PATHOPHYSIOLOGY**—portal hypertension → unknown substance reaches pulmonary vasculature causing vasoconstriction → findings similar to primary pulmonary hypertension
- **DIAGNOSIS**—echocardiogram, right heart catheterization
- **TREATMENTS**—O_2, diuretics, sildenafil, prostaglandins, calcium channel blockers, liver transplant

HEPATORENAL SYNDROME

- **PATHOPHYSIOLOGY**—liver failure → dilated systemic circulation → ↑ renin–aldosterone system with ↑ cardiac output but not enough to counter splanchnic vasodilatation → pre-renal failure. Type I is more serious, defined as >50% reduction of CrCl to ≤20 mL/min in ≤2 weeks or >2× increase in creatinine to >220 µmol/L [>2.2 mg/dL]. Patients are usually oligouric or anuric. Type II includes patients not meeting criteria for type I and is characterized by ascites resistant to diuretics
- **DIAGNOSIS**—a clinical diagnosis of exclusion; rule-out other etiologies of acute kidney injury (including pre-renal causes, ATN, infection, and GI bleed). Typically, urine Na <10 mM (<10 mEq/L), bland U/A, oliguria, and minimal improvement in renal function after volume expansion with IV albumin (1 g/kg/d and up to 100 g/d × 2 days)
- **TREATMENTS**—stop diuretics, fluid (usually no response), albumin, vasoconstrictors (midodrine, octreotide, norepinephrine), TIPS, renal replacement therapy, liver transplant

FLOOD SYNDROME (SPONTANEOUS UMBILICAL HERNIA RUPTURE)

- **PATHOPHYSIOLOGY**—liver failure → portal hypertension → ascites → umbilical hernia (up to 20%) → spontaneous rupture (rare)
- **PROGNOSIS**—50% mortality with supportive care, 10–20% mortality with urgent surgical repair

Related Topics
Acute Hepatic Failure (p. 143)
Ascites (p. 153)
Encephalopathy (p. 152)
Hemochromatosis (p. 482)
Hepatitis B (p. 145)
Hepatitis C (p. 147)
Jaundice (p. 155)

Hepatic Encephalopathy NEJM 1997 337:7

DIFFERENTIAL DIAGNOSIS

DRUGS
- **ALCOHOL**—acute intoxication, withdrawal, Wernicke–Korsakoff
- **PSYCHOACTIVE**—benzodiazepines, cocaine, heroine, ecstasy
- **OTHERS**—salicylates

INFECTIOUS—spontaneous bacterial peritonitis, pneumonia, UTI, meningitis, encephalitis, abscess

METABOLIC
- **ORGAN FAILURE**—hepatic, azotemia, hypothyroidism, hypoxemia, CO_2 narcosis
- **ELECTROLYTES**—ketoacidosis, hyponatremia, hypomagnesemia, hypercalcemia, glucose (hypo, hyper)

STRUCTURAL
- **HEMORRHAGE**—subarachnoid, epidural, subdural, intracerebral
- **STROKE**—basilar
- **TUMOR**
- **EPILEPSY**

NEUROPSYCHIATRIC

PATHOPHYSIOLOGY

GRADING OF HEPATIC ENCEPHALOPATHY
- **1**—reversed sleep cycle, mild confusion, tremor, incoordination
- **2**—lethargy or irritability, disoriented to time, asterixis, ataxia
- **3**—somnolence or agitation, disoriented to place, asterixis, hyperreflexia, positive Babinski
- **4**—coma, decerebrate

PRECIPITANTS OF HEPATIC ENCEPHALOPATHY
- ↑ **NH_4** —↑ protein intake, constipation, GI bleed, transfusion, infection (spontaneous bacterial peritonitis), azotemia, hypokalemia
- ↑ **DIFFUSION ACROSS BLOOD–BRAIN BARRIER**—alkalosis
- ↓ **METABOLISM**—dehydration, hypotension, hypoxemia, anemia, portosystemic shunt, hepatoma, progressive liver damage

CLINICAL FEATURES

HISTORY—characterize confusion (onset, duration, fluctuation), infectious symptoms, neurological symptoms, precipitants (diet, hydration, constipation, GI bleed, infection), past medical history (liver disease, alcohol and illicit drug use), medication history (sedatives, narcotics, missed lactulose)

PHYSICAL—vitals, signs of chronic liver disease, rectal examination (if suspect GI bleed), neurological examination, check for asterixis

INVESTIGATIONS

BASIC
- **LABS**—CBCD, lytes, urea, Cr, glucose, TSH, AST, ALT, ALP, bilirubin, INR, PTT, NH_4 (poorly correlated with degree of encephalopathy), Ca, Mg, PO_4, osmolality, CK, troponin (as part of delirium workup), urinalysis
- **MICROBIOLOGY**—blood C&S, urine C&S, sputum Gram stain/C&S
- **IMAGING**—US abd, CT abd
- **ASCITIC FLUID ANALYSIS**—cell count and diff, C&S to rule out SBP

SPECIAL
- **CT HEAD**—delirium workup
- **ABG**—if critically ill
- **GASTROSCOPY**—to check for varices
- **LIVER BIOPSY**
- **EEG**—symmetric, high voltage, slow wave pattern

MANAGEMENT

ACUTE HEPATIC ENCEPHALOPATHY
- **WORKUP FOR SEPSIS**
- **SYMPTOM CONTROL**—correct hypokalemia, if present. ***Lactulose*** 30 g PO BID–QID PRN titrate to 2–4 bowel movements/day; if patient obtunded and NPO, consider lactulose 300 mL (mixed with 700 mL of H_2O or NS) PR via rectal balloon catheter QID until awake. Consider sedation (*haloperidol* 1–2 mg PO/IV/SC q6h and q1h PRN) and ventilation, *mannitol* 1 g/kg 20% solution, acetylcysteine, epoprostenol
- **TREAT UNDERLYING CAUSE**—liver transplant

CHRONIC HEPATIC ENCEPHALOPATHY
- **SYMPTOM CONTROL**—protein restriction no longer routinely recommended. ***Lactulose*** 30 g PO BID–QID PRN titrate to 2–4 bowel movements/day. **Prophylaxis** with ***metronidazole*** 800 mg PO daily (associated peripheral neuropathy), ***neomycin*** 500–2000 mg PO TID (associated ototoxicity and nephrotoxicity), or ***rifaximin*** 550 mg PO BID (in high-risk patients with ≥2 episodes of hepatic encephalopathy in last 6 months). **Others** (*H. pylori* treatment, ornithine aspartate, branched amino acids)
- **TREAT UNDERLYING CAUSE**—liver transplant

Related Topic
Delirium (p. 432)

Ascites

NEJM 2004 350:16

DIFFERENTIAL DIAGNOSIS

↑ HYDROSTATIC PRESSURE

- **CARDIAC**—right heart failure, tricuspid regurgitation, constrictive pericarditis
- **HEPATIC**—**presinusoidal** (portal vein thrombosis, schistosomiasis), **sinusoidal** (cirrhosis), **postsinusoidal** (Budd–Chiari, veno-occlusive)

↓ ONCOTIC PRESSURE—malnutrition, liver disease, nephrotic syndrome, protein-losing enteropathy

DIFFERENTIAL DIAGNOSIS (CONT'D)

↑ CAPILLARY PERMEABILITY/LYMPHATIC OBSTRUCTION

- **INFECTIONS**—spontaneous bacterial peritonitis
- **MALIGNANCY**—ovarian, peritoneal metastasis
- **PANCREATITIS**

OTHERS—hypothyroidism

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE ASCITES?

	Sens	Spc	LR+	LR–
History				
↑ abdominal girth	87%	77%	4.1	0.17
Recent weight gain	67%	79%	3.2	0.42
Ankle swelling	93%	68%	2.8	0.10
Hepatitis	67%	79%	3.2	0.42
Heart failure	47%	73%	2.0	0.73
Alcoholism	60%	58%	1.4	0.69
Hx of carcinoma	13%	85%	0.91	1.01
Physical				
Fluid wave	62%	90%	5.3	0.6
Shifting dullness	77%	72%	2.1	0.4
Flank dullness	84%	59%	1.7	0.4
Bulging flanks	81%	59%	1.8	0.5

APPROACH—the most useful finding for making a diagnosis of ascites is a positive fluid wave. The most useful findings to rule out ascites are a negative history of ankle swelling or increased abdominal girth. Puddle sign and auscultatory percussion not recommended

JAMA 1992 267:19

The Rational Clinical Examination. McGraw-Hill, 2009

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, amylase, lipase, TSH, urinalysis
- **IMAGING**—US abd, CT abd
- **PARACENTESIS**—cell count + diff, Gram stain, C&S, AFB, albumin, LDH, glucose, amylase, triglyceride, cytology

SPECIAL

- **LAPAROSCOPY WITH PERITONEAL BIOPSY**

DIAGNOSTIC ISSUES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE BACTERIAL PERITONITIS OR PORTAL HYPERTENSION? HOW DO I PERFORM A PARACENTESIS AND ANALYZE THE RESULTS?

PARACENTESIS TECHNIQUE—two studies showed that testing for coagulation prior to paracentesis was probably unnecessary; one study showed that a 15-gauge, 3.25-in. needle-cannula was associated with less multiple

DIAGNOSTIC ISSUES (CONT'D)

peritoneal punctures and termination due to poor fluid return as compared to a 14-gauge needle in therapeutic paracentesis; one study showed immediate as compared to delayed inoculation of culture bottles improved diagnostic yield (100% vs. 77%); nine studies examined therapeutic paracentesis with or without albumin or nonalbumin plasma expanders and found no consistent effect on morbidity or mortality

FEATURES SUGGESTIVE OF SPONTANEOUS BACTERIAL PERITONITIS

	LR+	LR–
Ascitic fluid WBC/PMN		
Ascitic fluid WBC >1000 cells/μL	9.1	0.25
Ascitic fluid WBC >500 cells/μL	5.9	0.21
Ascitic fluid WBC >250 cells/μL	0.9	1.1
Ascitic fluid PMN >500 cells/μL	10.6	0.16
Ascitic fluid PMN >250 cells/μL	6.4	0.20
Ascitic fluid pH and blood ascitic pH gradient		
Ascitic fluid pH <7.31	4.1	0.47
Ascitic fluid pH <7.32	4.8	0.65
Ascitic fluid pH ≤7.31	5.8	0.43
Ascitic fluid pH <7.35	9.0	0.31
Ascitic fluid pH <7.40	2.5	0.23
Blood ascitic fluid pH gradient >0.11	4.6	0.47
Blood ascitic fluid pH gradient >0.10	7.1	0.30
Blood ascitic fluid pH gradient ≥0.10	11.3	0.12

FEATURES SUGGESTIVE OF PORTAL HYPERTENSION

	LR+	LR–
Serum ascites albumin gradient (SAAG)		
Serum-ascites albumin gradient ≥11 g/L (≥1.1 g/dL)	4.6	0.06

APPROACH—"ascitic fluid should be inoculated into blood culture bottles at the bedside. Spontaneous bacterial peritonitis is more likely at predescribed parameters of ascitic WBC count (>1000 cells/μL), PMN count (>250 cells/μL) or blood–ascitic fluid pH (<7.35), and portal hypertension is less likely below a predescribed serum-ascites albumin gradient (<11 g/L [<1.1 g/dL])"

JAMA 2008 299:10

DIAGNOSTIC ISSUES (CONT'D)

PARACENTESIS PROCEDURE—**NEJM 2006 355:E21**

SERUM-ASCITES ALBUMIN GRADIENT (SAAG)

- **PORTAL HYPERTENSION OR CONGESTIVE HEART FAILURE**—(serum albumin – ascites albumin) ≥11 g/L [≥1.1 g/dL]. To distinguish between portal hypertension and HF, consider checking for ascitic fluid total protein level (generally >25 g/L [>2.5 g/dL] in cardiac ascites due to normal leaky hepatic sinusoid, while portal hypertension is associated with "capillarized" sinusoids that are less leaky)
- **INFLAMMATORY**—(serum albumin – ascites albumin) <11 g/L [<1.1 g/dL]

MANAGEMENT

SYMPTOM CONTROL—**Na restriction** (88 mmol/day or 2 g/day. Check urine Na for compliance, i.e. <77 mmol/day). **Fluid restriction** (<1.5 L/day only if Na <120 mmol/L). **Diuretics** (*spironolactone* 100–400 mg PO daily and *furosemide* 40–160 mg PO daily, stepwise increase). **Paracentesis. Albumin** (if >5 L ascitic fluid removed, then replace with albumin. In general, give 100 mL of 25% albumin for every 3 L of ascites removed over 5 L), TIPS, liver transplant

TREAT UNDERLYING CAUSE—stop alcohol consumption

SPECIFIC ENTITIES

DIFFERENTIAL DIAGNOSIS OF ANASARCA—renal (nephrotic syndrome), cardiac (HF, tricuspid regurgitation, constrictive pericarditis), liver (cirrhosis), thyroid (hypothyroidism), malignancy (venous/lymphatic obstruction)

SPONTANEOUS BACTERIAL PERITONITIS (SBP)

- **PATHOPHYSIOLOGY**—overgrowth of bacteria in bowel (usually *E. coli*) → bacterial translocation (migration) across bowel wall → infect ascites. Usually in patients with cirrhosis and large volume ascites with low ascites protein. Symptoms may be subtle as the visceral peritoneum is separated from the parietal peritoneum. Important to differentiate SBP from perforated bowel causing peritonitis
- **CLINICAL FEATURES**—may be asymptomatic if detected early. Common signs and symptoms include fever, abdominal pain and tenderness (diffuse, continuous), diarrhea, confusion, or renal deterioration. Sepsis with hypotension and paralytic ileus may develop later

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—paracentesis (ascitic fluid PMN ≥250 cells/μL, fluid protein <10 g/L [<1.0 g/dL], Gram stain, C&S), blood cultures, urine cultures. (Note that in peritonitis secondary to perforated viscous, the ascitic fluid protein is usually >10 g/L [>1.0 g/dL], glucose <2.8 mmol/L [<51 mg/dL], and LDH > upper limit of normal, and polymicrobial)

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—*cefotaxime* 2 g IV q8h (preferred) or *ceftriaxone* 2 g IV q24h × 5–10 days, *albumin* 1.5 g/kg IV within 6 h of detection, then 1 g/kg IV on day 3 (reduces mortality and incidence of hepato-renal syndrome). **Secondary prophylaxis** include *ciprofloxacin* 750 mg PO weekly, *norfloxacin* 400 mg PO daily, or *trimethoprim–sulfamethoxazole* DS 1 tab PO daily

Jaundice

DIFFERENTIAL DIAGNOSIS OF JAUNDICE/ HYPERBILIRUBINEMIA

PRE-HEPATIC (hemolysis)
- **RBC MEMBRANE**—spherocytosis, elliptocytosis
- **RBC ENZYMES**—G6PD, pyruvate kinase deficiency
- **RBC HEMOGLOBIN**—sickle cell
- **BLOOD**—toxins, drugs (fludarabine), infections (malaria), immune
- **VASCULAR**—mechanical valve, vasculitis, HUS/TTP/DIC, HELLP, severe hypertension
- **INEFFECTIVE ERYTHROPOIESIS**—megaloblastic anemia

HEPATIC
- ↓ **UPTAKE**—Gilbert's, drugs (rifampin, contrast)
- ↓ **CONJUGATION**—Gilbert's, Crigler–Najjar I/II, hepatocellular diseases, drugs (chloramphenicol)
- ↓ **EXCRETION** (cholestasis)—Dubin–Johnson, Rotor, benign recurrent cholestasis, cholestasis of pregnancy, drug-induced cholestasis, PBC, PSC, TPN
- **MIXED**—hepatocellular disease, sepsis

POST-HEPATIC
- **GALLSTONES**
- **CANCER**—pancreas, bile ducts, ampulla
- **BILIARY STRUCTURES**—post-cholecystectomy, PSC, biliary atresia

PATHOPHYSIOLOGY

CHOLESTASIS—any condition in which bile excretion from the liver is blocked, which can occur either in the intrahepatic bile ducts (hepatic causes) or in the extrahepatic bile ducts (post-hepatic causes)

CLINICAL FEATURES

HISTORY—characterize jaundice (duration, previous episodes), abdominal pain, abdominal mass, stool color, urine color, pruritus, weight loss, past medical history (liver disease, hepatitis risk factors, IBD/PSC, hereditary disorders), medications

PHYSICAL—signs of chronic liver disease, liver and spleen examination

JAUNDICE—becomes clinically evident at levels of bilirubin >70 μmol/L [>41 mg/dL]

DARK URINE—suggests conjugated hyperbilirubinemia

PALE STOOL/PRURITUS—suggests cholestasis (bile cannot be secreted into the biliary system)

PAIN—painful jaundice suggests acute obstruction (by stones, masses); investigate with US abd/ERCP/MRCP/EUS. Painless jaundice suggests pancreatic cancer, infiltration, PSC, PBC, and drugs; investigate with imaging + biopsy

INVESTIGATIONS

BASIC
- **LABS**—CBCD, peripheral smear, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin (conjugated and unconjugated), INR, albumin, HAV IgM, HAV IgG, HBsAg, HBsAb, HBcIgM, anti-HCV, ANA, antismooth muscle antibody (ASMA), anti-mitochondrial antibody (AMA), ferritin, ceruloplasmin, α1-antitrypsin, AFP, LDH, haptoglobin, peripheral smear, reticulocyte counts
- **IMAGING**—US, CT abd

SPECIAL
- **ENDOSCOPIC US**
- **MRCP**
- **ERCP**
- **LIVER BIOPSY**

MANAGEMENT

TREAT UNDERLYING CAUSE

SPECIFIC ENTITIES

PRIMARY BILIARY CIRRHOSIS (PBC)

- **PATHOPHYSIOLOGY**—autoimmune destruction of intrahepatic bile ducts → cholestasis → inflammation and necrosis → cirrhosis
- **CLINICAL FEATURES**—pruritus, fatigue, RUQ pain, xanthelasmas, sicca syndrome, hyperlipidemia. Females >> males. With disease progression, symptoms of liver failure may be seen. Decreased bone mineral density
- **DIAGNOSIS**—antimitochondrial antibody (sens 95%), ANA (40%), ↑ bilirubin, ↑ ALP, ↓ C4, ↑ IgM, hyperlipidemia (cholesterol, rather than TG, is what classically becomes elevated). Liver biopsy can be helpful for staging but is not essential for diagnosis. Consider DEXA scan
- **TREATMENTS**—*ursodeoxycholic acid (ursodiol)* 13–15 mg/kg/day PO in 2–4 divided doses with food. Ursodeoxycholic acid has been shown to improve liver enzymes, slow disease progression (for stages I and II), delay time to transplant but does not treat pruritus. For pruritus, consider cholestyramine, rifampin, and naltrexone. Consider treating hyperlipidemia (despite hypercholesterolemia, risk of atherosclerotic death not increased). Prevent osteoporosis with calcium and vitamin D. Also provide supplement with fat-soluble vitamins (KADE), which are not well absorbed in cholestasis. Consider liver transplant if rising bilirubin, liver decompensation, refractory pruritus, or severe bone disease

NEJM 2007 357:15

PRIMARY SCLEROSING CHOLANGITIS (PSC)

- **PATHOPHYSIOLOGY**—cholangitis → fibrosis with intra-and extrahepatic duct strictures → cirrhosis; 75% associated with ulcerative colitis, 10% with cholangiocarcinoma
- **DIAGNOSIS**—MRCP, ERCP (beading, strictures), biopsy
- **TREATMENTS**—liver transplant

Acute Pancreatitis NEJM 1994 330:17

CAUSES

★BAD HITS★
BILIARY STONES
ALCOHOL
DRUGS—thiazides, furosemide, sulfonamide, tetracycline, calcium, estrogen, vinca alkaloids, antiretrovirals (didanosine, pentamidine)
HYPER—hypercalcemia, hyperlipidemia (V, I, IV)
INFECTIOUS—*E. coli*, HIV, CMV, mumps, ascariasis
IDIOPATHIC
INHERITED—familial
TRAUMA—blunt
SURGERY—ERCP (± sphincterotomy, 5% risk), sphincter of Oddi dysfunction

PATHOPHYSIOLOGY

COMPLICATIONS OF ACUTE PANCREATITIS
★SCAR★
Sepsis
Calcium (hypocalcemia)
Abdominal (necrotizing pancreatitis ± hemorrhage, pancreatic pseudocyst ± hemorrhage [10–20%], pancreatic abscess, splenic vein thrombosis, fistula, cholangitis
Respiratory failure (ARDS) and aspiration pneumonia
Renal failure

CLINICAL FEATURES

HISTORY—abdominal pain, nausea and vomiting, fever, anorexia, past medical history (previous pancreatitis, recent ERCP, biliary stones, alcohol use, HIV), medication history (diuretics, antibiotics)
PHYSICAL—vitals, volume status, abdominal examination, Cullen's sign (periumbilical ecchymoses suggestive of hemoperitoneum), Grey Turner's sign (ecchymoses of the flanks suggestive of retroperitoneal hemorrhage), Fox's sign (ecchymoses parallel and inferior to inguinal ligament along upper thighs suggesting retroperitoneal hemorrhage), Bryant's sign (blue scrotum suggesting retroperitoneal hemorrhage)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, LDH, lipase, amylase, Ca, albumin, fasting lipid profile
- **IMAGING**—US abd, CT abd (+ contrast for necrotic pancreatitis)
- **ERCP**—both diagnostic and therapeutic to relieve obstruction

DIAGNOSTIC AND PROGNOSTIC ISSUES

DIFFERENTIAL DIAGNOSIS FOR LIPASE ELEVATION—acute pancreatitis, pancreatic cancer, pancreatic duct obstruction, perforated peptic ulcer, bowel infarction, intestinal obstruction, renal failure

RANSON'S CRITERIA

- **ON ADMISSION**—age >55, WBC $>16 \times 10^9$/L, glucose >11.1 mmol/L [>200 mg/dL], AST >250 U/L, LDH >350 U/L
- **48 H**—hematocrit ↓ >10%, urea ↑ >1.78 mmol/L [>5 mg/dL], base deficit >4 mEq/L, Ca <2 mmol/L [<8 mg/dL], sequestration of fluid >6 L
- **PROGNOSIS**—0–2 = 2% mortality, 3–4 = 15%, 5–6 = 50%, 7–8 = 100%

MANAGEMENT

ACUTE—ABC, O_2, **IV hydration**. NPO, NG if severe N&V or obstruction. ***Morphine*** 2.5–5 mg SC q4h PRN and 1–2 mg IV q1h PRN (for theoretical concern of morphine-causing sphincter of Oddi spasm, some consider using Demerol instead). **Antiemetics** (*dimenhydrinate* 50 mg 2IM/IV q4h, *metoclopramide* 10 mg IV q4h).

MANAGEMENT (CONT'D)

Consider broad-spectrum **antibiotics** (*meropenem* 1 g IV q8h or *imipenem* 500 mg IV q6h) if infected necrosis suspected

NUTRITION SUPPORT—enteral or parenteral. Early aggressive nutrition may not be warranted

TREAT UNDERLYING CAUSE—**gallstone pancreatitis** (ERCP and biliary sphincterotomy within 72 h, cholecystectomy). **Necrotizing pancreatitis** (ICU admission, surgical debridement)

SPECIFIC ENTITIES

ASCENDING CHOLANGITIS

- **PATHOPHYSIOLOGY**—biliary calculi (choledocholithiasis), post-ERCP, tumors, primary sclerosing cholangitis, or benign stricture → biliary obstruction and stasis → bacterial colonization and infection (*E. coli*, *Klebsiella, Enterobacter*, *Enterococcus*, anaerobes) → liver failure, sepsis
- **CLINICAL FEATURES**—Charcot's triad consists of fever, right upper quadrant pain, and jaundice. Reynold's pentad is associated with the addition of hypotension and confusion
- **DIAGNOSIS**—↑ bilirubin, ALP, and potentially AST and ALT. Blood cultures essential. US abd to check for common bile duct dilatation and stones, ERCP (diagnostic and therapeutic)
- **TREATMENTS**—**antibiotics** (*meropenem* 1 g IV q8h, *imipenem* 500 mg IV q6h, or ampicillin plus gentamicin). **Facilitate biliary drainage** (urgent ERCP with sphincterotomy for infection source control, stone extraction, stent insertion, percutaneous transhepatic cholangiogram [PTC] with stent drainage, and surgical decompression as last resort)

6
HEMATOLOGY

Michael H. Kroll

Polycythemia

DIFFERENTIAL DIAGNOSIS

SPURIOUS—stress (Gaisböck's syndrome), decreased intravascular volume
PRIMARY—polycythemia rubra vera
SECONDARY ★HERA★

- **HYPOXIA**—obstructive sleep apnea, COPD, smoking, high altitude
- **EPO-SECRETING TUMORS**—renal, hepatoma, cerebellar, pheochromocytoma
- **RENAL**—polycystic kidney disease, hydronephrosis, post-transplant
- **ADRENAL**—Cushing's syndrome

PATHOPHYSIOLOGY

DEFINITION OF POLYCYTHEMIA—hematocrit >0.6 in ♂, hematocrit >0.5 in ♀

Related Topics
Hypoxemia (p. 102)
Myeloproliferative Disorders (p. 184)

CLINICAL FEATURES

HISTORY—hyperviscosity (headache, blurred vision, epistaxis), dyspnea, epigastric pain, early satiety, weight loss, fever, night sweats, pruritus, erythromelalgia, recent travel to high-altitude areas, past medical history (respiratory diseases, myeloproliferative disorders, myocardial infarction, stroke, pulmonary embolism, DVT, renal disorders, smoking), medications (androgens, EPO)
PHYSICAL—hypertension, oxygen saturation, facial plethora, conjunctival injections, engorgement of the veins of the optic fundus, abdominal mass, hepatomegaly, splenomegaly, excoriations, stigmata of a prior arterial or venous thrombotic event, gouty arthritis, and tophi

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, leukocyte alkaline phosphatase (LAP), vitamin B12, RBC mass (total blood volume × Hct, to rule out spurious causes), carboxyhemoglobin level, cortisol level, peripheral blood smear
- **IMAGING**—CXR

SPECIAL

- **JAK2 MUTATION**—JAK2 is a cytoplasmic tyrosine kinase activated by EPO binding to its receptor; the V617F mutation activates JAK2 and thereby drives EPO-independent erythropoiesis. JAK2 mutation >95% sensitive for primary PRV
- **EPO LEVEL**—low in PRV, high if secondary causes
- **HYPOXIA WORKUP**—oximetry, ABG, CO-hemoglobin
- **SOLID TUMOR WORKUP**—CT abd, MRI head (if tumors)
- **BONE MARROW BIOPSY**—rule out myelofibrosis and CML

DIAGNOSTIC ISSUES

CRITERIA FOR POLYCYTHEMIA RUBRA VERA (PRV)

- **ABSOLUTE**—↑ RBC mass, no secondary cause (normal PaO_2, EPO not elevated)
- **MAJOR**—splenomegaly, JAKV617F
- **MINOR**—WBC $>12 \times 10^3/\mu L$, platelet $>400 \times 10^3/\mu L$
- **DIAGNOSIS**—need absolute criteria plus one major or two minor criteria for the diagnosis of polycythemia rubra vera. See myeloproliferative disorders (p. 184) for more details

D. Hui et al. (eds.), *Approach to Internal Medicine: A Resource Book for Clinical Practice*,
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MANAGEMENT

TREAT UNDERLYING CAUSE—**relative** (hydration), **CO hemoglobinemia** (smoking cessation. See p. 480), **sleep apnea** (CPAP. See p. 20), **polycythemia vera** (cytoreduction with hydroxyurea

MANAGEMENT (CONT'D)

is preferable to phlebotomy target to keep hematocrit <0.45 in ♂ and <0.42 in ♀, *ASA* 81 mg PO daily prevents thrombosis—but watch out for bleeding)

Microcytic Anemia NEJM 2005 352:10

DIFFERENTIAL DIAGNOSIS

★TAILS★

THALASSEMIA

ANEMIA OF CHRONIC DISEASE—infection, malignancy, inflammatory disorders

IRON DEFICIENCY—blood loss (GI, GU, vaginal, trauma), iron-deficient diet, celiac disease, atrophic gastritis, renal failure on EPO, pulmonary hemosiderosis, intravascular hemolysis

LEAD POISONING

SIDEROBLASTIC

PATHOPHYSIOLOGY

DEFINITION OF MICROCYTIC ANEMIA—Hb <135 g/L [<13.5 g/dL], MCV <80 fL

SEQUENCE OF IRON DEFICIENCY—↓ iron → ↑ TIBC → ↓ Hb → ↓ MCV → hypochromia

ANEMIA OF CHRONIC DISEASE—chronic inflammatory states such as malignancy, infection and rheumatologic diseases → ↑ INFγ, TNFα, IL-1, IL-6, IL-10 → ↑ hepatic expression of hepcidin which inhibits duodenal absorption of iron, ↑ uptake and storage of iron into monocytes and macrophages, ↓ production of EPO → ↓ availability of iron for erythrocytes → anemia (microcytic or normocytic)

CLINICAL FEATURES

HISTORY—shortness of breath, chest pain, dizziness, fatigue, bleeding (GI, menstrual), pica (ice, dirt), diet history, fever, night sweats, weight loss, past medical history (malignancy, chronic infections, rheumatologic disorders), medications (NSAIDs, ASA, anticoagulants), family history (thalassemia)

PHYSICAL—vitals, koilonychia (spoon nails), alopecia, blue sclerae, conjunctival pallor, angular cheilitis, atrophic glossitis, lymphadenopathy (anemia of chronic disease), rectal examination for occult blood and pelvic examination for blood loss

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, reticulocyte count, serum iron, serum ferritin, TIBC (transferrin), % sat, Hb electrophoresis, fecal occult blood (if suspect GI bleed)

SPECIAL

- **ENDOSCOPY**—gastroscopy and/or colonoscopy targeting symptoms in any man or post-menopausal woman with iron deficiency or in anyone with suspected GI bleeding
- **SOLUBLE TRANSFERRIN RECEPTOR** (sTfR)—helps to distinguish between iron deficiency and anemia of chronic disease. Depleted iron stores is associated with increased sTfR levels
- **BONE MARROW ASPIRATE AND BIOPSY WITH IRON STAIN**

DIAGNOSTIC ISSUES

IRON INDICES

	Ferritin	Iron	TIBC	% sat
Iron deficiency	↓	↓	↑	↓
Anemia of chronic disease	↑/N	↓	N/↓	N/↓
Thalassemia	↑/N	↑	↓	↑
Sideroblastic	N/↑	N/↓	N/↓	N/↓

DISTINGUISHING FEATURES BETWEEN IRON DEFICIENCY AND THALASSEMIA

- **RDW**—red cells in thalassemia tend to have a narrower distribution than in iron deficiency
- **MCV**—red cells in thalassemia tend to be smaller than in iron deficiency
- **RBC**—RBC high or normal if thalassemia but tend to decrease proportionally to Hb in iron deficiency

DIAGNOSTIC ISSUES (CONT'D)

- **THALASSEMIA INDEX**—MCV/RBC. Suggests thalassemia if <13 and iron deficiency if >13
- **MORPHOLOGY**—thalassemia causes microcytic target cells

DISTINGUISHING FEATURES BETWEEN IRON DEFICIENCY AND ANEMIA OF CHRONIC DISEASE—ferritin is indicative of marrow iron stores and is key to the diagnosis of iron deficiency anemia as serum iron and TIBC levels may change with other diseases. Ferritin may be elevated as acute phase reactant

- **<30 ng/ml**—iron deficiency anemia (PPV 92–98%)
- **30–100 ng/ml**—combination of anemia of chronic disease and true iron deficiency if (sTfR/log ferritin) > 2. Anemia of chronic disease alone if (sTfR/log ferritin) <1
- **100 ng/ml**—anemia of chronic disease

MANAGEMENT

SYMPTOM CONTROL—**transfusion** 1–2 U PRBC IV over 2 h for symptom control

TREAT UNDERLYING CAUSE—**iron deficiency** (*iron gluconate* 300 mg PO BID, *iron sulfate* 325 mg PO BID, *sodium ferric gluconate* complex in sucrose 125 mg IV, iron sucrose 200 mg IV, *ferumoxytol* 510 mg IV). It may take up to 6 weeks to correct anemia and 6 months to replete iron stores

SPECIFIC ENTITIES

PLUMMER–VINSON SYNDROME—iron deficiency anemia, atrophic glossitis and esophageal web. Increased risk of esophageal squamous cell carcinoma

Normocytic Anemia

DIFFERENTIAL DIAGNOSIS

ACUTE BLOOD LOSS—GI, GU, pelvis/abdomen, skin, CNS

↓ PRODUCTION

- **PRIMARY MARROW DISORDERS**—bone marrow suppression from drugs (esp. chemotherapy), multiple myeloma, myelodysplasia, myeloproliferative disorders, lymphoma, metastasis, infections (esp. TB)
- **DECREASED EPO**—renal failure
- **ANEMIA OF CHRONIC DISEASE**

SEQUESTRATION—splenomegaly

↑ DESTRUCTION

- **IMMUNE**—autoimmune hemolytic anemia (warm IgG antibody, cold IgM agglutinins)
- **NON-IMMUNE**
  - **RBC MEMBRANE**—spherocytosis
  - **RBC ENZYMES**—G6PD, pyruvate kinase deficiency
  - **RBC HEMOGLOBIN**—sickle cell anemia
  - **MICROANGIOPATHIC**—DIC, HUS/TTP, prosthetic valve, hypertensive crisis
  - **BLOOD**—toxins, infections (malaria), immune

MIXED PICTURE—combined microcytic and macrocytic anemia (e.g. malnutrition causing iron deficiency and vitamin B12 deficiency)

PATHOPHYSIOLOGY

DEFINITION OF NORMOCYTIC ANEMIA—Hb <135 g/L [<13.5 g/dL], MCV 80–100 fL

CLINICAL FEATURES

HISTORY—shortness of breath, chest pain, dizziness, fatigue, bleeding, fever, night sweats, weight loss, diet history, past medical history (malignancy, chronic infections, rheumatologic disorders, liver disease, renal disease, alcohol, hypothyroidism, myelodysplasia), medications (NSAIDs, ASA, chemotherapy, antibiotics, antiepileptics), family history (sickle cell)

PHYSICAL—vitals, jaundice, conjunctival pallor, cardiac examination, liver examination. Check for macroglossia, subacute combined degeneration and peripheral neuropathy. Rectal examination for occult blood

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, reticulocyte count, iron, ferritin, TIBC, % sat, Cr, TSH, AST, ALT, ALP, bilirubin, INR, PTT, haptoglobin, LDH, direct and indirect Coombs test, serum protein electrophoresis, fecal occult blood

SPECIAL

- **URINE TESTS**—urinalysis (hemoglobinuria)
- **BONE MARROW ASPIRATE AND BIOPSY**

DIAGNOSTIC ISSUES

MCHC—↑ MCHC suggests spherocytosis

MCV—a rise in MCV suggests reticulocytosis; ↑↑↑ MCV indicates the presence of cold agglutinins

DIAGNOSTIC ISSUES (CONT'D)

causing agglutination in the laboratory specimen before blood is run through the analyzer

COOMBS TEST

- **DIRECT COOMBS TEST** (DAT)—patient's washed RBC incubated with anti-IgG and anti-C3. A positive result (i.e. agglutination) indicates that IgG and/or C3 have bound to RBC surface in vivo. DAT positivity suggests immune rather than nonimmune causes of hemolysis
  - **IMMUNE HEMOLYTIC ANEMIA** (DAT positive)—autoimmune hemolytic anemia, drug-induced hemolytic anemia, alloimmune hemolytic anemia (acute hemolytic reaction)
  - **NON-IMMUNE HEMOLYTIC ANEMIA** (DAT negative)—TTP/HUS, DIC, hemoglobinopathies, hereditary spherocytosis
- **INDIRECT COOMBS TEST**—normal RBC incubated with patient's serum. It is mainly used to detect low concentrations of antibodies in a patient's serum prior to blood transfusion

RETICULOCYTE PRODUCTION INDEX (RPI, corrected reticulocyte count)—more accurate than raw reticulocyte count to evaluate if bone marrow response to anemia is appropriate or hypoproliferative

- **RPI** = [retic count × (hematocrit in %/45)]/maturation factor

Maturation Factor	Hematocrit
1.0%	45%
1.5%	35%
2.0%	25%
2.5%	20%

- **INTERPRETATION**—RPI >2% suggests adequate marrow response, < 2% suggests hypoproliferative (i.e. ↓ production)

MANAGEMENT

TREAT UNDERLYING CAUSE

SYMPTOM CONTROL—**transfusion** 2 U PRBC IV over 2 h. **Erythropoietin** (*epoetin alfa* 50–200 U/kg/week SC/IV div 2–3×/week, *darbepoetin alfa* 20–40 μg SC weekly) for anemia of chronic kidney disease or selected patients on active chemotherapy (after ensuring iron stores replete)

MANAGEMENT (CONT'D)

SPECIFIC ENTITIES

AUTOIMMUNE HEMOLYTIC ANEMIA: WARM ANTIBODY—IgG

- **CAUSES**—**neoplasia** (CLL, especially with fludarabine, pentostatin, cladribine), **autoimmune** (SLE), **infections** (viral), **drugs** (penicillins, fludarabine, methyldopa)
- **CLINICAL FEATURES**—anemia, jaundice, splenomegaly, smear (microspherocytosis), ↑ reticulocytes, ↑ bilirubin, ↑ LDH, ↓ haptoglobin, direct Coombs test (IgG±, C3±)
- **TREATMENTS**—**symptom control** (transfusion with caution, difficult to cross-match due to autoantibodies reacting with antigens present on cells of almost all individuals). **Steroids** (prednisone 1 mg/kg PO daily, taper after stable). **Reduce antibody-mediated clearance** (IVIG, splenectomy). **Immunosuppression** (*azathioprine* 100–150 mg PO daily, *cyclophosphamide* 100 mg PO daily). **Biological agents** (rituximab, alemtuzumab). **Treat underlying disease** (CLL, SLE, drugs)

AUTOIMMUNE HEMOLYTIC ANEMIA COLD AGGLUTININS—IgM

- **CAUSES**—**neoplasia** (CLL, lymphoma, Waldenstrom's macroglobulinemia, adenocarcinoma), **infections** (mycoplasma pneumonia, infectious mononucleosis, CMV, VZV)
- **CLINICAL FEATURES**—anemia, agglutination, jaundice, splenomegaly, smear (spherocytosis), ↑ reticulocytes, ↑ bilirubin, ↑ LDH, ↓ haptoglobin, direct Coombs test (IgG–, C3+), cold agglutinin screen
- **TREATMENTS**—**symptom control** (avoidance of cold). **Steroids** (*prednisone* 1 mg/kg PO daily, taper after stable). **Chemotherapy** (cyclophosphamide, chlorambucil). **Biological agents** (rituximab, INFα). **Plasmapheresis**

Macrocytic Anemia

DIFFERENTIAL DIAGNOSIS

LIVER DISEASE

ALCOHOL

DRUGS—**chemotherapy** (hydroxyurea, cytosine arabinoside, methotrexate, azathioprine, cladribine, capecitabine), **antiepileptics** (phenytoin, phenobarbital), **antibiotics/antivirals** (trimethoprim–sulfamethoxazole, zidovudine)

VITAMIN B12 DEFICIENCY FROM PERNICIOUS ANEMIA

DIETARY FOLATE DEFICIENCY

DIFFERENTIAL DIAGNOSIS (CONT'D)

DIFFERENTIAL DIAGNOSIS (CONT'D)

MYELODYSPLASTIC SYNDROME
PAROXYSMAL NOCTURNAL HEMOGLOBINURIA
HYPOTHYROIDISM
RETICULOCYTOSIS

PATHOPHYSIOLOGY

DEFINITION OF MACROCYTIC ANEMIA—Hb <135 g/L [<13.5 g/dL], MCV >100 fL

Related Topics
Alcoholism (p. 117)
Chronic Liver Disease (p. 149)
Myelodysplastic Syndrome (p. 187)
Vitamin B12 Deficiency (p. 459)

CLINICAL FEATURES

HISTORY—shortness of breath, chest pain, dizziness, fatigue, bleeding, fever, night sweats, weight loss, diet history, past medical history (liver disease, alcohol, hypothyroidism, myelodysplasia), medications (chemotherapy, antibiotics, antiepileptics)
PHYSICAL—look for signs of hypothyroidism, vitamin B12 deficiency and chronic liver disease. Vitals (bradycardia, hypoventilation, hypotension), leukonychia, clubbing, Dupuytren's contractures, palmar erythema, asterixis, cool and dry skin, vitiligo, hair thinning, alopecia areata, periorbital edema, scleral icterus, conjunctival pallor, altered mental status, macroglossia, parotid enlargement, fetor hepaticus, goiter, lymphadenopathy, spider angiomas, gynecomastia, pericardial effusion, ascites, splenomegaly, caput medusa, hemorrhoids, testicular atrophy, proximal muscle weakness, hyporeflexia, edema (non-pitting), petechiae, subacute combined degeneration of the cord (B12 deficiency affecting dorsal columns and lateral corticospinal tracts, test for Romberg sign, vibration and proprioception), peripheral neuropathy

INVESTIGATIONS

BASIC
- **LABS**—CBCD, peripheral smear, reticulocyte count, vitamin B12, RBC folate, TSH, AST, ALT, ALP, bilirubin, INR, PTT

SPECIAL
- **UGI ENDOSCOPY**—to identify atrophic gastritis and survey for gastric cancer
- **BONE MARROW BIOPSY**

MANAGEMENT

SYMPTOM CONTROL—**transfusion** 2 U PRBC IV over 2 h in everyone except those with pernicious anemia. For patients with pernicious anemia, transfuse fewer units and transfuse each unit slowly over 3 h since an expanded intravascular volume puts patients at risk for transfusion-induced pulmonary edema
TREAT UNDERLYING CAUSE—**folate deficiency** (*folate* 0.4 mg PO/SC/IM daily × 4–5 days). **Vitamin B12 deficiency** (*vitamin B12* 1,000 µg PO/SC/IM daily × 5–10 days, then 1,000 µg PO/SC/IM qweek × 4 weeks, then every month). **Hypothyroidism** (*levothyroxine* start 12.5–50 µg PO daily, adjust every 2 weeks)

Sickle Cell Disease

PATHOPHYSIOLOGY

β-CHAIN MUTATION—leads to formation of hemoglobin S ($\alpha 2\beta S2$) → polymerization of hemoglobin S → elongated fibers that distort shape of RBC → vasoocclusive phenomena (infarctions, ischemia) and hemolysis. Subtypes include **sickle cell disease** (homozygous HbS, most severe), **hemoglobin SC disease** (heterozygous HbS and HbC, moderately severe) and **sickle cell trait** (heterozygous HbS, mild)

CLINICAL FEATURES

★ABCDEFGH PAIN★
ANEMIA
- **CHRONIC HEMOLYSIS**—normo or macrocytic due to reticulocytosis, elevated bilirubin, LDH, low haptoglobin). There may be associated folate/iron deficiency from increased utilization
- **ACUTE ANEMIA**—may be due to splenic sequestration crisis (venoocclusion of spleen leading to RBC pooling), aplastic crisis (transient arrest of erythropoiesis), and hyperhemolytic crisis (sudden onset of severe hemolysis). All of these may be triggered by viral infections such as parvovirus B19

BONES—bone infarction (pancytopenia), avascular necrosis, fat embolism, orbital compression syndrome
CARDIAC—myocardial infarction (due to increased oxygen demand from cardiac output)

CLINICAL FEATURES (CONT'D)

DERMATOLOGIC—leg ulcers
EYES—proliferative retinopathy, retinal artery occlusion, retinal detachment and hemorrhage
FAIRLY BAD PAIN—back, chest, extremities and abdomen. May be associated with fever, swelling, tenderness, tachypnea, hypertension, nausea, and vomiting. May be precipitated by weather changes, dehydration, infection, stress, menses and alcohol. Multi-organ failure may develop in severe pain episodes
GENITAL—priapism
HEPATOSPLENIC—splenic infarction, acute hepatic ischemia, hepatic or splenic sequestration crisis, iron overload (transfusions)
PULMONARY—restrictive lung disease (chronic interstitial fibrosis), obstructive lung disease, hypoxemia, pulmonary hypertension, fat embolism
ANEMIA—remember that sickle cell disease is associated with both acute and chronic anemia
INFECTIONS—sepsis (particularly asplenic patients), meningitis, pneumonia, osteomyelitis (susceptible to Salmonella and gram negative osteomyelitis)
NEUROLOGIC—ischemic stroke, intracerebral hemorrhage, septic emboli, spinal cord infarction or compression, vestibular dysfunction, sensory hearing loss, cognitive failure

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, LDH, haptoglobin, smear (sickled red cells, polychromasia from reticulocytosis, Howell–Jolly bodies from hyposplenia), reticulocytes, RBC folate, Fe, ferritin, % saturation, transferrin, hemoglobin electrophoresis (identify subtypes), urinalysis
- **MICROBIOLOGY**—blood C&S, sputum Gram stain/AFB/C&S, urine C&S, stool C&S, O&P, C. diff toxin A/B

MANAGEMENT

ACUTE—ABC, O_2, IV

- **VASOOCCLUSIVE PAIN CRISIS**—fluids, pain control (morphine, ketorolac)
- **APLASTIC CRISIS**—transfusions. Avoid GCSF
- **SEQUESTRATION CRISIS**—fluids, judicious transfusion if symptomatic anemia to avoid overload if trapped splenic blood re-enters circulation
- **HEMOLYTIC CRISIS**
- **ACUTE CHEST SYNDROME** (chest pain, pulmonary infiltrates, cough, progressive anemia, hypoxemia, with or without fever)—treat precipitating factor, fluids, pain control, transfusions (simple or exchange)
- **PRIAPISM**—hydration, analgesics, transfusions, urology consultation
- **PREOPERATIVELY**—transfuse to Hb 100 g/L [10 g/dL]

CHRONIC—interprofessional team, **immunizations** (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Niesseria meningitidis*, hepatitis B virus, and influenza), **exchange transfusion** (goal HbS < 30%), ***hydroxyurea*** (increase levels of fetal Hb, decrease incidence of vasoocclusive pain), ***folic acid*** 1 mg PO daily

SPECIFIC ENTITIES

ASPLENIC PATIENTS—particularly susceptible to encapsulated bacteria (*S. pneumoniae*, *H. influenzae*, and *N. meningitidis*), *Capnocytophaga canimorsus*, Gram-negative enteric organisms, and babesiosis

- **VACCINATIONS**—all patients should receive vaccinations against *H. influenzae*, pneumococcus, and meningococcus. Flu shot should be given annually and other immunizations repeated every 5 years
- **ANTIBIOTICS WITH FEVER**—any fever in an asplenic patient should prompt self-administration of preprescribed antibiotics (*levofloxacin* 750 mg PO daily, *moxifloxacin* 400 mg PO daily, or *cefuroxime* 1 g PO daily). Patients should then seek medical advice urgently
- **MEDICAL ALERT BRACELET**

Neutropenia

DIFFERENTIAL DIAGNOSIS

★PANIC★
POST-INFECTIOUS—sepsis
AUTOIMMUNE—drug induced, SLE
NEOPLASTIC—lymphoproliferative disorders, myelodysplasia, leukemias, myelophthisis
INFECTIONS—sepsis, HIV
INSUFFICIENCY—folate, vitamin B12

DIFFERENTIAL DIAGNOSIS (CONT'D)

IATROGENIC—chemotherapy, chloramphenicol, trimethoprim–sulfamethoxazole, synthetic penicillins, phenytoin, carbamazepine, NSAIDs, gold, antithyroid medications, phenothiazines, clozapine
CONSUMPTION—hypersplenism

Related Topic
Febrile Neutropenia (p. 263)

PATHOPHYSIOLOGY

DEFINITION OF NEUTROPENIA—neutrophils $<1.5\times10^3/\mu L$, severe neutropenia if absolute neutrophil count (ANC) $<0.5\times10^3/\mu L$

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, peripheral smear, PTT, INR, AST, ALT, ALP

SPECIAL

- **FURTHER WORKUP**—bilirubin, fibrinogen, LDH, ANA, vitamin B12, RBC folate
- **BONE MARROW BIOPSY**

MANAGEMENT

TREAT UNDERLYING CAUSE

GROWTH FACTORS—in some cases, the use of myeloid growth factors such as G-CSF or GM-CSF is appropriate

TREATMENT ISSUES

FEBRILE VS NON-FEBRILE NEUTROPENIA—the presence of fever (>38.3 °C [>101 °F] or >38 °C [>100.4 °F] sustained >1 h) in a neutropenic patient is considered an emergency, as overwhelming sepsis can develop quickly. Patients with febrile neutropenia (see p. 263 for definition) require early evaluation, initiation of antibiotics, and potentially hospitalization. However, neutropenia alone without fever can usually be monitored on an outpatient basis. Isolation is usually not required, although patients should avoid the following: (1) being in contact with people with active infections, (2) consumption of uncooked meat/vegetables and unpasteurized dairy products and (3) exposure to fresh flowers or plants

SPECIFIC ENTITIES

ETHNIC NEUTROPENIA—neutrophil counts in blacks are generally lower. Neutrophil count may be down to $1.5\times10^3/\mu L$ and still be considered normal

Eosinophilia

DIFFERENTIAL DIAGNOSIS

★PAIN★

PRIMARILY ORGAN-SPECIFIC DISORDERS

- **PULMONARY**—interstitial lung disease, AIDS-related pneumonia, idiopathic eosinophilic pneumonia, drug-induced lung disease
- **GASTROINTESTINAL**—eosinophilic gastroenteritis, eosinophilic esophagitis, primary biliary cirrhosis, primary sclerosing cholangitits
- **GENITOURINARY**—acute interstitial nephritis, acute post-streptococcal glomerulonephritis, eosinophilic cystitis, eosinophilic prostatitis
- **RHEUMATOLOGIC**—eosinophilia–myalgia syndrome and idiopathic eosinophilic synovitis, Churg–Strauss syndrome
- **DERMATOLOGIC**—eosinophilic panniculitis, episodic angioedema with eosinophilia, Kimura disease and angiolymphoid hyperplasia with eosinophilia, eosinophilic fasciitis, eosinophilic cellulitis, eosinophilic pustular folliculitis, recurrent cutaneous necrotizing eosinophilic vasculitis, eosinophilic ulcers of the oral mucosa

ALLERGIES

- **NASAL**—allergic rhinitis, asthma, nasal polyposis

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **MEDICATIONS**—**cytokine mediated** (GM-CSF, IL-2), **pulmonary** (NSAIDs), **gastroenteritis** (NSAIDs), **interstitial nephritis** (penicillins, cephalosporins), **necrotizing myocarditis** (ranitidine), **vasculitis** (phenytoin, allopurinol), **asymptomatic** (ampicillin, penicillins, cephalosporins)

ADRENAL—adrenal insufficiency

ATHEROEMBOLIC—cholesterol emboli

INFECTIONS

- **PARASITIC**—angiostrongyliasis costaricensis, ascariasis, hookworm, strongyloidiasis, trichinosis
- **FUNGAL**—aspergillosis, coccidioidomycosis
- **OTHERS**—chronic TB, scarlet fever, HIV related

NEOPLASTIC

- **HEMATOLOGIC**—hypereosinophilic syndrome, Hodgkin's lymphoma, non-Hodgkin's lymphoma, mastocytosis
- **SOLID TUMOR**—**large cell carcinoma** (lung), **squamous cell carcinoma** (vagina, penis, skin, nasopharynx), **adenocarcinoma** (stomach, large bowel, uterine body), **transitional cell carcinoma**

PATHOPHYSIOLOGY

DEFINITION OF EOSINOPHILIA—eosinophils >600/μL

EOSINOPHIL FUNCTION—eosinophils play an important role in both combating infections (especially parasitic) and allergic response, through the release of cytotoxic molecules, reactive oxygen species, and cytokines. Thus, common causes of eosinophilia include infections and allergies

CLINICAL FEATURES

HISTORY—dyspnea, chest pain, cough, sputum, diarrhea, rash, fever, lymphadenopathy, weight loss, night sweats, infectious contact, travel history, past medical history (allergic rhinitis, asthma), medications (NSAIDs, antibiotics, phenytoin, allopurinol), allergies

PHYSICAL—vitals (hypotension, fever), rash, weight loss, nasal, lymphadenopathy, respiratory examination, abdominal examination

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, AST, ALT, ALP, bilirubin, CK, ESR, C3, C4, ANCA, serology for parasites
- **MICROBIOLOGY**—blood C&S, urine C&S, stool C&S, stool O&P
- **IMAGING**—CXR, CT chest

SPECIAL

- **BRONCHOSCOPY**—if pulmonary eosinophilia

DIAGNOSTIC ISSUES

PERIPHERAL EOSINOPHIL COUNTS—as eosinophils are primarily tissue dwelling, they are likely several hundred-fold more abundant in affected tissues than represented in peripheral blood. Furthermore, the development of an intercurrent bacterial or viral infection may lead to suppression of blood eosinophilia until the superimposed acute infection has resolved. Thus, elevated or even normal blood eosinophil counts in a febrile patient should prompt investigations for eosinophilia (e.g. adrenal insufficiency)

MANAGEMENT

SYMPTOM CONTROL

TREAT UNDERLYING CAUSE—**deworm** (if parasites), **stop offending drugs** (if suspect medication induced), **prednisone** (if unknown cause), **hydroxyurea or imatinib** (for idiopathic hypereosinophilic syndrome)

SPECIFIC ENTITIES

PULMONARY EOSINOPHILIA

- **PATHOPHYSIOLOGY**—defined as ↑ eosinophils in blood with evidence of lung involvement, radiologically, through bronchoalveolar lavage or lung biopsy
- **CAUSES**—**infectious** (Loeffler's syndrome [*Ascaris*, hookworms, strongyloides], *Paragonimus* lung flukes, tropical pulmonary eosinophilia [*Wuchereria bancrofti*, *Brugia malayi*], coccidioidal), **medications** (NSAIDs, nitrofurantoin, ampicillin, minocycline, phenytoin, ranitidine), **idiopathic** (acute eosinophilic pneumonia, chronic eosinophilic pneumonia), **others** (Churg–Strauss, allergic bronchopulmonary aspergillosis)

Thrombocytosis NEJM 2004 350:12

DIFFERENTIAL DIAGNOSIS

PRIMARY (clonal thrombocytosis)—essential thrombocythemia, chronic myelogenous leukemia, polycythemia rubra vera, myeloid metaplasia with or without myelofibrosis, prefibrotic myelofibrosis

SECONDARY (reactive)

- **MALIGNANCY**
- **INFECTIONS**
- **CONNECTIVE TISSUE DISEASE**
- **DRUG REACTIONS**—vincristine, all-trans-retinoic acid, cytokines, growth factors

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **OTHERS**—iron deficiency, acute blood loss, hemolytic anemia, rebound from thrombocytopenia, splenectomy

PATHOPHYSIOLOGY

DEFINITION—platelets >450 × 10^3/μL

Related Topic
Myeloproliferative Disorders (p. 184)

CLINICAL FEATURES

DISTINGUISHING FEATURES BETWEEN PRIMARY AND SECONDARY THROMBOCYTOSIS

	Primary	Secondary
Underlying disease	N	Y
Digital ischemia/CVA	Y	N
Thrombosis	Y	N
Bleeding	Y	N
Splenomegaly	Y (40%)	N
Peripheral smear	Giant platelets	Normal platelets
Platelet function	Abnormal	Normal
BM megakaryocytes	↑, giant	↑, normal

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, PTT, INR, Fe, ferritin, TIBC, % sat, ESR (secondary cause), CRP (secondary cause)

SPECIAL

- **BONE MARROW BIOPSY**

DIAGNOSTIC ISSUES

IMPORTANT PEARL—remember that essential thrombocythemia is a diagnosis of exclusion. Thus, it is important to consider and rule out iron deficiency, occult malignancy, and another myeloproliferative disorder before making this diagnosis

MANAGEMENT

ESSENTIAL THROMBOCYTHEMIA—observation if asymptomatic and low risk of thrombosis, defined as age <60 and no cardiovascular risk factors. For all others with platelet counts $>450\times10^3/\mu L$, use ***ASA*** 81 mg PO daily (low dose) plus **hydroxyurea** (or **anagrelide**) targeting normalization of the platelet count. When the platelets are $>1{,}500\times10^3/\mu L$, **plateletpheresis** must be started for active ischemia and can be considered for use in asymptomatic patients at risk for coronary and/or cerebral ischemic events

SECONDARY CAUSES—treat underlying cause

Thrombocytopenia

DIFFERENTIAL DIAGNOSIS

PSEUDOTHROMBOCYTOPENIA—platelet clumping (usually due to EDTA-induced platelet activation, recollect with citrate)

DILUTIONAL—PRBC transfusion (at least 15–20 units), pregnancy

↓ PRODUCTION

- **INFILTRATIVE**—leukemia, MDS, bone marrow metastasis
- **INFECTIONS**—HIV, rubella, mumps, varicella, parvovirus, HCV, EBV
- **APLASIA**—aplastic anemia, Fanconi anemia
- **TOXINS**—chemotherapy, radiation, alcohol
- **B12/FOLATE DEFICIENCY**

HYPERSPLENISM—congestive, reactive, infiltrative (see SPLENOMEGALY p. 182)

↑ DESTRUCTION

- **IMMUNE THROMBOCYTOPENIC PURPURA**—primary, secondary (lymphoma, CLL, HIV, SLE, Evans syndrome)
- **ALLOIMMUNE**—neonatal, post-transfusion, post-transplantation

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **MICROANGIOPATHIC HEMOLYTIC ANEMIA**—disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), HELLP syndrome, antiphospholipid antibody syndrome
- **INFECTIONS**—HIV, EBV, CMV
- **MEDICATIONS**—heparin, GPIIb/IIIa inhibitors, quinine, quinidine, valproic acid, thiazides, sulfonamides, rifampin, indomethacin, vancomycin, linezolid

PATHOPHYSIOLOGY

DEFINITION—platelets $<150\times10^3/\mu L$. However, an acute drop of 50%, even if the platelet count remains in the normal range, requires close monitoring and potential investigations

LIFE CYCLE—half-life of platelets is 8–10 days. One-third of the total body platelets is found in the spleen

PATHOPHYSIOLOGY (CONT'D)

BLEEDING RISK IN UNDER-PRODUCTION THROMBOCYTOPENIA

Platelet count ($\times 10^3/\mu L$)	Bleeding risk
>100	Minimal symptoms
50–100	Minor symptoms
10–50	Prone to bruises
<10	Risk of spontaneous bleed (intracranial bleed)

NOTE: in destruction or sequestration thrombocytopenia, bleeding does not correlate with the magnitude of thrombocytopenia

CLINICAL FEATURES

HISTORY—mucocutaneous bleeding (epistaxis, petechiae, easy bruising), abdominal pain, bloody diarrhea, recent infections, fever, weight loss, past medical history (malignancy, HIV, ITP, alcohol), medications (heparin, GPIIb/IIIa inhibitors, quinine, ASA, NSAIDs)

PHYSICAL—vitals. Look for retinal bleed (fundoscopy), petechiae, and purpura. Check for lymphadenopathy and hepatosplenomegaly

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, peripheral smear, PTT, INR, AST, ALT, ALP, bilirubin, fibrinogen, LDH, ANA, vitamin B12, RBC folate, D-dimer, HIV serology, hepatitis serology, Coombs test

SPECIAL

- **HITT ASSAY**—heparin-induced platelet aggregation assay, heparin–PF4 solid phase immunoassay, serotonin release assay
- **BONE MARROW BIOPSY**

DIAGNOSTIC ISSUES

SMEAR

- **LARGE PLATELETS**—destruction (ITP), sequestration
- **SCHISTOCYTES/FRAGMENTS**—microangiopathic hemolytic anemia (DIC, TTP)

BONE MARROW BIOPSY

- **DECREASED MEGAKARYOCYTES**—underproduction
- **INCREASED MEGAKARYOCYTES**—destruction/sequestration/MDS (5q- syndrome)

MANAGEMENT

SYMPTOM CONTROL—in under-production thrombocytopenia, **transfuse** 5 U platelets if platelets $<50\times10^3/\mu L$ and severe bleeding, platelets $<10\times10^3/\mu L$ in non-bleeding patient, and prior to certain procedures (expect platelet rise of ~5/unit). 1-h post-transfusion platelet count can help differentiate under-production vs. destructive causes. Note that platelet transfusions are not effective in ITP and may worsen TTP/HUS and HITT

TREAT UNDERLYING CAUSE—**discontinue medications** that may cause thrombocytopenia (platelets may return to normal in 7–14 days). Please refer to specific disorders below for details regarding treatment of each disease

SPECIFIC ENTITIES

MICROANGIOPATHIC HEMOLYTIC ANEMIA (MAHA)—also called fragmentation hemolysis. Characterized by non-immune hemolytic anemia with schistocytosis. Causes include DIC, HELLP, TTP, HUS, malignancy, malignant hypertension, artificial heart valve, insertion of foreign bodies, and medications

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

- **PATHOPHYSIOLOGY**—damage to endothelium → release of tissue factor → massive activation of coagulation cascade → intravascular coagulation and depletion of clotting factors
- **CAUSES**—trauma, shock, sepsis (*Escherichia coli*, *N. meningitidis*, malaria), neoplasm (lung, prostate, pancreatic), obstetrical (abruptio placentae, preeclampsia, amniotic fluid embolus)
- **CLINICAL FEATURES**—microangiopathic hemolytic anemia, thrombocytopenia, bleeding and/or thrombosis, ischemia. ↑ INR, ↑ PTT, ↓ fibrinogen (although it can be normal or even elevated in acute phase), ↑ D-dimers, ↓ factor VIII (in contrast to liver diseases, which have normal factor VIII). Schistocytes on peripheral smear
- **TREATMENTS**—**treat underlying cause and complications** (hypoxia, dehydration, acidosis, acute renal failure). **Replete coagulation factors** (FFP) **and fibrinogen** (cryoprecipitate) **if deficient and bleeding. Anticoagulation if thrombosis** (consider IV heparin 200–500 IU/h infusion)

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

- **PATHOPHYSIOLOGY**—↓ ADAMTS13 activity → failure to degrade unusually large multimers of vWF → agglutination of platelets → arteriolar

SPECIFIC ENTITIES (CONT'D)

thrombi → systemic ischemia of brain, kidneys, gut, and heart
- **CAUSE**—autoantibody to ADAMTS13
- **CLINICAL FEATURES**—MAHA (100%), thrombocytopenia (90%), renal dysfunction, fever (90–100%), neurologic abnormalities (90%) with delirium, focal neurological deficit, seizure, coma. Schistocytes on peripheral smear
- **TREATMENTS**—full volume plasma exchange (plasmapheresis + FFP infusions), steroids, and rituximab if not resolving. Avoid platelet transfusion, ASA and antimotility agents. High mortality without treatment

NEJM 2006 354:18

HEMOLYTIC UREMIC SYNDROME (HUS)
- **PATHOPHYSIOLOGY**—exposure to Shiga toxin or defect in plasma factor H → arteriolar thrombi → predominantly renal involvement
- **CAUSES**—*E. coli* O157:H7
- **CLINICAL FEATURES**—MAHA (100%), thrombocytopenia (90%), renal dysfunction (90%). Schistocytes on peripheral smear
- **TREATMENTS**—supportive care only. Does not respond to plasma exchange. Avoid antibiotics unless patient septic.

Related Topics
Anticoagulation Therapy (p. 178)
Antiphospholipid Antibody Syndrome (p. 175)
Thrombocytopenia in Pregnancy (p. 477)

HEPARIN-INDUCED THROMBOCYTOPENIA AND THROMBOSIS (HITT)
- **PATHOPHYSIOLOGY**—**type I** (non-immune) happens within 2 days, mild drop in platelets, and return to normal by itself. **Type 2** (immune) starts between days 4 and 14 (can present earlier if recent heparin exposure in past 1–3 months). It is usually more severe (platelet drop >50%) and has great clinical significance. Pathogenesis: heparin complexes with PF4 (from platelets) → IgG against heparin–PF4 complex → these megacomplexes bind to platelets and activate them, producing more PF4 → platelet aggregation → thrombosis
- **CAUSES**—heparin, LMWH (much less likely)
- **CLINICAL FEATURES** (type II)—thrombocytopenia, thrombosis, ischemia
- **TREATMENTS** (type II)—**stop heparin immediately and treat with danaparoid**, **lepirudin**, **or argatroban** until platelets return to normal. Begin warfarin when platelets $>150\times10^3/\mu L$ and overlap warfarin with the alternative anticoagulant for 5 days (this reduces risk of venous limb gangrene). Avoid future heparin exposure except during CABG (performed at least 3 months after heparin exposure)

IMMUNE THROMBOCYTOPENIA (ITP)
- **PATHOPHYSIOLOGY**—autoantibodies against platelets → isolated thrombocytopenia
- **ASSOCIATIONS**—neoplasm (CLL, lymphoma), infections (HIV), autoimmune (SLE)
- **DIAGNOSIS**—isolated thrombocytopenia with an otherwise normal CBC and no obvious causes
- **TREATMENTS**—should be started when platelets $<20\times10^3/\mu L$. The goal of treatment is to support platelet counts until spontaneous remission occurs
  - **URGENT SUPPORT**—given to patients with active bleeding. ***IVIG*** 1 g/kg IV daily × 1–2 days, which may increase the platelet count within days and lasts for a few weeks. ***Methylprednisolone*** 1 g IV daily × 3 days. **Platelet transfusions** may also provide temporary support for actively bleeding patients
  - **FIRST LINE**—***prednisone*** 1–2 mg/kg PO daily until platelet count returns to normal. Platelet recovery occurs within 3 weeks in 2/3 of patients. If platelet count did not increase after 4 weeks of treatment, consider second line therapies
  - **SECOND LINE**—**rituximab**, **thrombopoietic agents** (romiplostim, eltrombopag) **splenectomy**. See p. 163 for details on counseling of patients undergoing splenectomy
  - **OTHER OPTIONS**—chemotherapy (CVP), danazol. HAART for HIV-associated ITP

NEJM 2002 346:13

EVANS SYNDROME—ITP and autoimmune hemolytic anemia

DRUG-INDUCED IMMUNE THROMBOCYTOPENIA—patients usually present with severe thrombocytopenia (platelets $<20\times10^3/\mu L$). With the exception of platelet inhibitors, there is usually 5–7 days between initiation of drug therapy and platelet drop if patient is receiving the medication for the first time. Treatment consists of discontinuation of offending (or all) drugs and platelet transfusions as needed

NEJM 2007 357:6

Pancytopenia

DIFFERENTIAL DIAGNOSIS

★PANIC★

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)—↑ complement-mediated red cell lysis

APLASTIC ANEMIA

- **IDIOPATHIC** (50%)
  - **INFECTIONS**—EBV, CMV, parvovirus, hepatitis
  - **FANCONI'S ANEMIA**
  - **DRUG INDUCED**—chemotherapy, gold
  - **TOXINS**—alcohol

NEOPLASTIC—leukemia (AML, CLL), MDS, bone marrow metastasis

INFECTIONS—sepsis, TB, *Parvovirus*, fungal

INSUFFICIENCY—folate, vitamin B12

IATROGENIC—chemotherapy

CONSUMPTION—hypersplenism, immune-mediated destruction

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, B12, RBC folate, HIV test, Coombs test

SPECIAL

- **BONE MARROW BIOPSY**—if suspect aplastic anemia or malignancy
- **FLOW CYTOMETRY**—if suspect PNH. Historically, sucrose hemolysis test used for screening, followed by Ham acid hemolysis test for diagnosis. Currently flow cytometry is used to measure the expression of the complement regulatory proteins CD55 and CD59, which are deficient on blood cells in PNH

DIAGNOSTIC ISSUES

PRE-MEDS FOR BONE MARROW BIOPSY—*morphine* 2.5–5 mg IV, *lorazepam* 1 mg SL, Elma cream

MANAGEMENT

TREAT UNDERLYING CAUSE

SPECIFIC ENTITIES

APLASTIC ANEMIA

- **PATHOPHYSIOLOGY**—precipitants (e.g. *Parvovirus*, drugs) → T-cell subsets produce local concentrations of INFγ → ↑ Fas on CD34+ cells (maturing stem cells) → apoptosis → severe pancytopenia and hypocellular marrow. Complications include paroxysmal nocturnal hemoglobinuria, acute leukemia, and MDS
- **TREATMENTS**—corticosteroids, antithymocyte globulin, cyclosporine, stem cell transplant

FANCONI'S ANEMIA—hereditary form of aplastic anemia that usually affects children but occasionally presents in adults. The main features include pancytopenia, hyperpigmentation, skeletal malformation, small stature, and hypogonadism

Bleeding Diathesis

DIFFERENTIAL DIAGNOSIS

★PVC★ platelets, **v**essels, **c**oagulopathy

EXTRINSIC PATHWAY (isolated PT/INR ↑)

- **FACTOR DEFICIENCY OR INHIBITOR**—VII or X
- **VITAMIN K DEFICIENCY**—malnutrition, pancreatic insufficiency, recent antibiotic use, warfarin use (early stage)
- **LIVER DISEASE**
- **EARLY DIC**

INTRINSIC PATHWAY (isolated PTT ↑)

- **FACTOR DEFICIENCY**—X-linked deficiency of factor VIII (hemophilia A) or factor IX (hemophilia B). Autosomal deficiency of factor XI, especially among Ashkenazi Jews (8% are carriers)
- **VON WILLEBRAND DISEASE**
- **FACTOR INHIBITORS**—lupus anticoagulant due to APA; acquired hemophilia due to an inhibitor to factor VIII
- **HEPARIN USE**

COMMON PATHWAY (PT ↑, PTT ↑)

- **FACTOR DEFICIENCY**—X, V, II, I
- **VITAMIN K DEFICIENCY**—malnutrition, pancreatic insufficiency, recent antibiotic use
- **LIVER DISEASE**

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **DIC**

PLATELET DYSFUNCTION (normal PT and PTT, platelet >90 × 10^3/μL, bleeding time ↑)

- **INHERITED**—Bernard–Soulier syndrome, Glanzmann's thrombasthenia, storage pool disease
- **ACQUIRED**—renal failure, liver failure, myeloproliferative disorders, paraproteinemias, autoantibodies, DIC, acquired storage pool disease from extracorporeal circulation

VESSELS—collagen vascular disease, scurvy

NOTE: INR = international normalized ratio, helps to standardize interpretation of PT

PATHOPHYSIOLOGY

HEMOSTASIS

- **PRIMARY HEMOSTASIS**—endothelium, platelets
- **SECONDARY HEMOSTASIS**—coagulation proteins

PLATELET ACTIVATION PATHWAY

1. Collagen binds to GPIa/IIa on platelet membrane, also binds to GPIb/IX via vWF
2. Platelet becomes activated by agonist binding (thrombin, adenosine diphosphate, epinephrine, collagen)
3. Secretion of δ granules (serotonin, ADP) and α granules (vWF, growth factors, factor V, factor X, fibrinogen)
4. Conformational change → phospholipids become available for factors V and VIII binding
5. Platelet aggregation (unstable) by vWF and fibrinogen binding to the activated GPIIb/IIIa complex
6. Platelet fibrin clot formation—fibrin–fibrin crosslinked by factor XIII and platelet–fibrin via GPIIb/IIIa

ANTICOAGULATION PATHWAYS

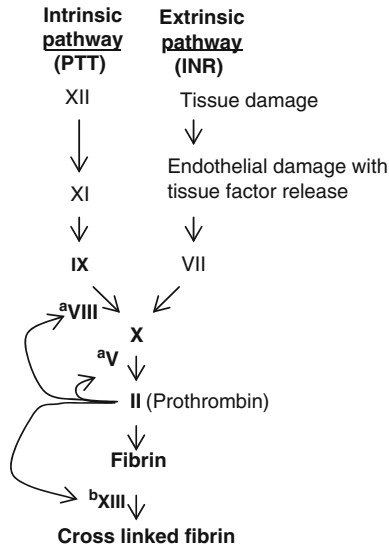
1. Antithrombin binds to thrombin and inhibits it
2. Thrombin binds to thrombomodulin which activates protein C and S to cleave factors Va and VIIIa
3. Factor Xa → tPA (by endothelial cells) → plasmin → fibrinolysis

COAGULATION FACTOR PEARLS

- **SYNTHESIZED IN LIVER**—factors I, II, V, VII, VIII, IX, X, XI, XII, protein C, S, AT-III, plasminogen
- **VITAMIN K DEPENDENT**—factors II, VII, IX, X, protein C, S
- **SYNTHESIZED IN ENDOTHELIAL CELLS AND MEGAKARYOCYTES**—vWF

PATHOPHYSIOLOGY (CONT'D)

COAGULATION PATHWAY



[a]Non-enzymatic cofactors; [b]Factor XIII is called "fibrin-stabilizing factor" because it covalently cross-links fibrin polymers and strengthens the clot

FACTORS VII AND VIII ARE SPECIAL

- **FACTOR VII**—shortest half-life (5–7 h). Decreased factor VII results in INR ↑. Thus, INR can help to detect *early* stages of liver failure, DIC, vitamin K deficiency, and warfarin use
- **FACTOR VIII**—part of coagulation cascade and has von Willebrand factor (vWF, synthesized by endothelial cells) as carrier in plasma. Thus, von Willebrand disease (vWD) leads to ↓ factor VIII

CLINICAL FEATURES

BLEEDING SYNDROMES

- **PLATELET DYSFUNCTION**—skin/mucous membrane (petechiae, purpura, small/superficial ecchymosis, epistaxis, gingival bleed, menorrhagia), immediate bleeding
- **COAGULATION FACTORS**—joints/muscles (hemarthroses, muscle hematomas, large/palpable ecchymosis), delayed bleeding

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, AST, ALT, ALP, bilirubin, albumin, PT/INR, PTT, D-dimer, fibrinogen

VWD	Inheritance	Pathophysiology
I	Heterozygous mutations	Mild to moderate quantitative ↓ of all multimers
IIA	Autosomal dominant/recessive	↓ activity of vWF due to decrease in large multimers of vWF (synthesis of active forms in platelet adhesion)
IIB	Autosomal dominant	Same as IIa except decrease due to large multimer vWF adherence to platelets
IIN	Autosomal recessive	↓ vWF affinity for factor VIII, similar to hemophilia
III	Homozygous mutations	Complete absence of vWF

INVESTIGATIONS (CONT'D)

SPECIAL

- **HEPZYME STUDY**—to remove heparin from blood samples to distinguish if isolated elevation of PTT is spurious
- **50:50 MIXING STUDY**—to distinguish between factor deficiency vs. inhibitors (factor deficiency corrects with mixing study)
- **HEMOPHILIA WORKUP**—factors VIII, IX, XI
- **ANTIPHOSPHOLIPID ANTIBODY SYNDROME WORKUP**—lupus anticoagulant screen, anticardiolipin antibody, dilute Russell's viper venom time, anti-β2 glycoprotein 1 antibody
- **VON WILLEBRAND DISEASE WORKUP**—von Willebrand factor (vWF) antigen levels, factor VIII level, ristocetin cofactor activity, ristocetin-induced platelet aggregation
- **PLATELET DISORDER WORKUP**—bleeding time, platelet aggregometry
- **MYELOMA WORKUP**—serum protein electrophoresis

MANAGEMENT

ACUTE—ABC, O_2, IV, **transfusion** 2 U **PRBC** IV over 2 h, transfusion **platelets** 6 U, **FFP** 15 mL/kg, **cryoprecipitate** 10–15 U q48h for fibrinogen deficiency

TREAT UNDERLYING CAUSE—**avoid** heparin, LMWH, warfarin. **Vitamin K deficiency** (*vitamin K* 10 mg PO/IV daily × 3 days; IV vitamin K replacement has risk of anaphylaxis). **vWD type I** (*DDAVP* 0.3 μg/kg SC, intermediate purity factor VIII)

SPECIFIC ENTITIES

VON WILLEBRAND DISEASE (VWD)

- **PATHOPHYSIOLOGY**—vWF acts as a linker between platelets and endothelium and also serves as carrier for factor VIII. Thus, vWD deficiency may lead to decrease in factor VIII levels
- **CLINICAL FEATURES**—platelet disorder with bruising, skin or mucosal bleeding, and heavy menstrual cycles for most subtypes, except type IIN which manifests as hemophilia with soft tissue, joint, and urinary bleeding
- **DIAGNOSIS**—**Ristocetin cofactor activity** (RCo, assesses capacity of plasma vWF to support ristocetin-induced aggregation of control platelets), **collagen binding activity** (assesses vWF binding to collagen), vWF antigen (non-functional assay that quantifies vWF), **vWF multimer assay** (agarose gel to determine the size of multimers), **ristocetin-induced platelet aggregation** (assesses vWF binding to platelets in patients' platelet-rich plasma)
- **TREATMENTS**—*DDAVP* 0.3 μg/kg by IV infusion or 300 μg one spray each nasal for type I patients. vWF concentrates containing all vWF multimers may be used for type II and III and for bleeding and surgical management of type 1 patients

BERNARD–SOULIER SYNDROME—mutation of GPIb/IX (platelet receptor for vWF)

GLANZMANN'S THROMBASTHENIA—mutation of GPIIb/IIIa (platelet receptor for fibrinogen)

STORAGE POOL DISEASE—defect in releasing platelet granules (especially ADP)

VWD	vWF:Ag	vWF:RCo	vWF multimer	RIPA
I	↓	↓	↓ all multimers	↓
IIA	↓ or N	↓	↓ large multimers	↓ or N
IIB	↓ or N	↓	↓ large multimers	↑
IIN	Normal	↓	Normal	Normal
III	↓↓	↓↓	↓↓ undetectable	↓↓

Hypercoagulable States

DIFFERENTIAL DIAGNOSIS

ANTICOAGULATION FACTORS

- **DEFICIENCY**—protein S, protein C, antithrombin III, plasminogen. Secondary causes of clotting factor deficiencies include HITT, DIC, TTP, HUS, PNH, APA, and nephrotic syndrome (reduced antithrombin III)
- **ALTERATION**—factor V Leiden, prothrombin G20210A mutations
- **EXCESS**—fibrinogen, hyperhomocysteinemia

VASCULAR DAMAGE—**vasculitis**, **sepsis**, **trauma**, **surgery**, **cancer** (Trousseau's syndrome, lymphoproliferative disease)

STASIS—bed rest, pregnancy, air travel, leg cast

PATHOPHYSIOLOGY

RISK FACTORS FOR VENOUS THROMBOEMBOLISM

- **COAGULATION FACTORS**—excess, mutation (factor V Leiden, prothrombin), deficiency (protein S, protein C, antithrombin III, plasminogen, tissue plasminogen activator)
- **NEOPLASTIC**—solid tumors, myeloproliferative, leukemia
- **OTHERS**—immobilization, surgery, congestive heart failure, oral contraceptives, hormone replacement therapy, pregnancy, nephrotic syndrome

RISK FACTORS FOR ARTERIAL THROMBOEMBOLISM

- **ATHEROSCLEROSIS**—hypertension, diabetes, smoking
- **EMBOLIC**—AF, atrial myxoma, endocarditis, cholesterol emboli, MI with ventricular thrombosis, paradoxical embolism
- **OTHERS**—SLE

RISK FACTORS FOR ARTERIAL AND VENOUS THROMBOEMBOLISM

- **FACTORS**—hyperhomocysteinemia, dysfibrinogenemia, plasminogen activator deficiency

PATHOPHYSIOLOGY (CONT'D)

- **PLATELET DEFECTS**—myeloproliferative disorders, HITT, PNH
- **HYPERVISCOSITY**—polycythemia rubra vera, Waldenstrom's macroglobulinemia, cryoglobulinemia, sickle cell disease
- **OTHERS**—antiphospholipid antibody syndrome, vasculitis, paradoxical embolism
- **BIOPROSTHETIC HEART VALVE**—low-level anticoagulation (INR 2–3) in first 3 months following valve replacement

NEJM 2002 346:10

FACTOR V LEIDEN—mutation that resists cleavage by activated protein C. Most common hereditary form of thrombophilia (3–4% general population)

THROMBOPHILIC MUTATIONS—antithrombin III, homozygous factor V Leiden > protein S, protein C > heterozygous factor V Leiden > prothrombin gene mutation in terms of risk of thrombosis

INVESTIGATIONS

BASIC

- **LABS**—CBCD, PT, INR, activated protein C resistance, factor V Leiden, prothrombin G20210A, anticardiolipin antibody, lupus anticoagulant, homocysteine, protein C, protein S, antithrombin III, fibrinogen, urinalysis
- **IMAGING**—CXR

SPECIAL

- **PREGNANCY TEST**—if female <50

Related Topics
Anticoagulation Therapy (p. 178)
DVT (p. 176)
Pulmonary Embolism (p. 10)

DIAGNOSTIC ISSUES

INDICATIONS FOR HYPERCOAGULABILITY WORKUP—testing for inherited thrombophilia is not routinely warranted in a patient with first episode unprovoked VTE. However, there may be benefit to investigating patients with a family history of VTE, unusual thrombosis (hepatic, portal, mesenteric, or cerebral veins), recurrent thromboembolism, or arterial thrombosis

THROMBOPHILIA WORKUP AFTER ACUTE THROMBOSIS OR DURING ANTICOAGULATION—acute VTE and anticoagulants can affect thrombophilia testing

Hypercoagulable Disorder	Acute Thrombosis	Heparin Anticoagulation	Warfarin Anticoagulation
Anti-thrombin deficiency	↓	↓	–
APLA	–	–	–
Lupus anticoagulant	–	Cannot measure	False positive
Factor V Leiden	–	–	–
Protein C and S	↓	–	Cannot measure
Prothrombin gene mutation	–	–	–

Draw protein C and S prior to warfarin therapy

MANAGEMENT

ACUTE—ABC, O_2 to keep sat >94%, IV, consider thrombolysis for systolic BP <90 mmHg for >15 min

ANTICOAGULATION—see Approach to Anticoagulation Table. For cancer patients, extended anticoagulation beyond the first 6 months is generally considered and LMWH preferred anticoagulant

IVC FILTER—when anticoagulation is contraindicated; use a retrievable filter if the contraindication is temporary

TREATMENT ISSUES

WARFARIN USE AND PROTEIN C DEFICIENCY—patients with protein C deficiency given warfarin may be susceptible to transient hypercoagulable state (coumadin necrosis). This can be avoided by overlapping heparin with warfarin for 5 days (with minimum 48 h therapeutic INR overlap)

PRIMARY PROPHYLAXIS OF THROMBOEMBOLISM IN HOSPITALIZED MEDICAL PATIENTS

- **INDICATIONS**—patients on the medical service >40-year old have limited mobility for ≥3 days, and have at least 1 of following risk factors
  - **CONDITIONS**—acute infectious disease, congestive heart failure, acute myocardial infarction, acute respiratory disease, stroke, rheumatic disease, inflammatory bowel disease, cancer
  - **CLINICAL CHARACTERISTIC**—previous venous thromboembolism, older age (especially >75), recent surgery or trauma, immobility or paresis, BMI >30 kg/m^2, inherited or acquired thrombophilic states, varicose veins, estrogen therapy
- **INTERVENTIONS**—early ambulation and exercises involving foot extension for all patients. Specific prophylaxis regimens include *heparin* 5,000 U SC q8h, *enoxaparin* 40 mg SC daily, *dalteparin* 5,000 U SC daily, or *fondaparinux* 2.5 mg SC daily. For patients at high risk for bleeding, consider non-pharmacologic measures such as graduated compression stockings and pneumatic compression devices

NEJM 2007 365:14

RISK REDUCTION BY ANTICOAGULATION

- **ACUTE VTE**—without anticoagulation, the risk for recurrent VTE is 50% Anticoagulation ↓ risk to 8–10% by 1 month and 4–5% by 3 months
- **VTE WITH LONG-TERM RISK FACTORS**—recurrent DVT risk 10%/year. Anticoagulation ↓ risk to <3%/year

TREATMENT ISSUES (CONT'D)

- **VTE IN PATIENTS WITH CANCER**—risk of recurrence at 6 months 17% with warfarin and 9% with *dalteparin* 200 IU/kg for 3 weeks, followed by 150 IU/kg for at least 6 months. LMWH is anticoagulant of choice in patients with malignancy
- **AF WITH PREVIOUS STROKE**—recurrent stroke risk 12%/year. Anticoagulation ↓ risk to < 4%/year
- **AF WITH OTHER RISK FACTORS**—recurrent stroke 8%/year. Anticoagulation ↓ risk to < 2%/year
- **LONE AF**—recurrent stroke risk 1–2%/year. Anticoagulation ↓ risk to < 1%/year

MECHANICAL HEART VALVE—recurrent arterial embolic risk 4%/year. Warfarin ↓ risk to < 1%/year. Mitral valve prostheses 2× risk of aortic valve prostheses. INR 2–3 for bileaflet or tilting disc mechanical valves and 2.5–3.5 for caged-ball or caged-disc valves

SPECIFIC ENTITIES

ANTIPHOSPHOLIPID ANTIBODY SYNDROME (APS)

- **PATHOPHYSIOLOGY**—antibody against phospholipids or cell surface proteins bound to anionic phospholipids. These include lupus anticoagulants, anticardiolipin antibody (false-positive VDRL), and anti-β2-glycoprotein 1 antibody → may lead to hypercoagulable state
- **CAUSES**—primary APS, secondary APS (various rheumatic diseases such as SLE and infections such as HIV and drugs)
- **CLINICAL FEATURES**—venous and arterial thrombosis and rarely hemorrhage affecting the lungs, heart, CNS, GI, kidneys, skin, and eyes. Also recurrent fetal losses (recurrent first trimester or single late term), thrombocytopenia, and livedo reticularis
- **DIAGNOSIS**—**clinical criteria** include thrombosis (≥1 arterial, venous, or small-vessel thrombosis in any organ) or pregnancy complications (≥1 unexplained deaths of morphologically normal fetus at or after the 10th week of gestation, ≥1 premature births of morphologically normal neonate at or before the 34th week of gestation, or ≥3 unexplained consecutive spontaneous abortions before the 10th week of gestation). **Laboratory criteria** include anti-

SPECIFIC ENTITIES (CONT'D)

cardiolipin or anti-β2-glycoprotein 1 antibodies (IgG or IgM at moderate or high levels on ≥2 occasions at least 6 weeks apart) or the presence of a lupus anticoagulant (≥2 occasions at least 6 weeks apart). Diagnosis requires at least one clinical and one laboratory criterion (sens 70%, spc 98%)

- **CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME**—acute and devastating syndrome with multiple simultaneous vascular occlusions throughout the body, affecting mainly small vessels of kidney, lungs, CNS, heart, and skin. May be associated with DIC, ARDS, cerebral and myocardial microinfarctions. May be precipitated by infections, surgery, and withdrawal of anticoagulation. Treatment consists of a combination of anticoagulation, steroids, plasmapheresis, and/or IVIG. Mortality rate is 50%
- **TREATMENTS**—primary prophylaxis for thrombosis is not indicated in persons with incidentally discovered antiphospholipid antibodies or lupus anticoagulants. Treatment of thromboses (both venous and arterial) is indefinite warfarin anticoagulation targeting an INR of 2–3. See p. 478 for management of APS in pregnancy

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

- **PATHOPHYSIOLOGY**—mutation in PIG-A gene coding for GPI anchor → ↓ GPI-linked proteins such as CD59 (membrane attack complex inhibitory factor) and CD55 (decay accelerating factor) → complement-mediated lysis of RBC → acute renal failure due to hemoglobulinuria, chronic renal failure due to iron deposits. Also ↑ platelet activation and endothelial injury due to complement activation, ↑ tissue factor, ↓ fibrinolysis → ↑ thrombosis
- **CLINICAL FEATURES**—hemolysis, venous thrombosis (hepatic vein, portal vein, splenic vein, renal vein), arterial thrombosis (rarer), marrow aplasia, MDS, leukemia, infections, esophageal spasm, sexual dysfunction
- **DIAGNOSIS**—flow cytometry, historically, Ham's test (RBC sensitivity to acidity)
- **TREATMENTS**—steroids, eculizumab (anti-complement protein 5), allogeneic stem cell transplant

Deep Vein Thrombosis

NEJM 2004 351:3

DIFFERENTIAL DIAGNOSIS OF UNILATERAL LEG SWELLING/DEEP VEIN THROMBOSIS

VASCULAR—DVT, venous insufficiency, superficial thrombophlebitis (chronic)
LYMPHATIC—lymphedema (chronic)
DRUGS—drug-induced edema (calcium channel blockers)
OTHER—cellulitis, necrotizing fasciitis, knee injury, calf muscle tear, Baker cyst rupture

PATHOPHYSIOLOGY

LOCATION—DVT typically originates in the venous sinuses of the calf muscles and occasionally the proximal veins. While most calf vein thrombi lyse spontaneously, ~15% extend into proximal veins within 2 weeks
COMPLICATIONS—clot extension, pulmonary embolism, recurrent thrombosis, post-thrombotic syndrome, chronic thromboembolic pulmonary hypertension

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, PTT, INR, D-dimer, fibrinogen, AST, ALT, ALP, bili
- **IMAGING**—doppler/compression US (sens 95%, spc 95%)

INVESTIGATIONS (CONT'D)

SPECIAL

- **THROMBOPHILIA WORKUP**—if there is a family history of thrombosis, consider activated protein C resistance, factor V Leiden, prothrombin G20210A, antithrombin III, protein C, and protein S
- **PREGNANCY TEST**—in female <50
- **VENOGRAM**—gold standard

DIAGNOSTIC ISSUES

COMPRESSION US—high sensitivity (95%) and specificity (95%) for DVT. US of calf veins is not routinely performed because of lower sensitivity (70%). Rather, US of thigh (deep veins) is usually repeated in 2 weeks after a normal test to detect the possible extension of DVT from calf into proximal veins

Related Topics
Anticoagulation Therapy (p. 178)
Hypercoagulable States (p. 173)
Pulmonary Embolism (p. 10)

RATIONAL CLINICAL EXAMINATION SERIES DOES THIS PATIENT HAVE DEEP VEIN THROMBOSIS? WELL'S CRITERIA FOR DVT
—alternative diagnosis more or as likely (−2), recent paralysis/paresis/plaster immobilization (+1), recent bedridden >3 days or major surgery <4 weeks (+1), localized tenderness along deep venous system (+1), calf swelling by more than 3 cm at 10 cm below tibial tuberosity (+1), pitting edema greater in symptomatic leg (+1), collateral non-varicose superficial veins (+1), active cancer (+1)

D-DIMER UTILITY FOR DVT BASED ON WELL'S CRITERIA

	Sens	Spc	LR+	LR−
Low risk	88%	72%	3.3	0.18
Moderate risk	90%	58%	2.1	0.19
High risk	92%	45%	1.6	0.16

Post-test Probability of DVT Using High Sensitivity D-dimer Assay
LOW RISK (0 or less points)—0.5% chance of DVT. If D-dimer negative, can exclude DVT
MODERATE RISK (1–2 points)—1% chance of DVT. Workup may or may not be needed
HIGH RISK (3 or greater points)—8.6% chance of DVT. D-dimer testing not useful. Proceed to compression US or impedance plethysmography → serial studies → venogram
APPROACH—"diagnostic accuracy for DVT improves when clinical probability is estimated before diagnostic tests. Patients with low clinical probability on the predictive rule have prevalence of DVT of <5%. In low-probability patients with negative D-dimer results, diagnosis of DVT can be excluded without ultrasound; in patients with high clinical suspicion for DVT, results should not affect clinical decisions"

JAMA 2006 295:2
The Rational Clinical Examination. McGraw-Hill, 2009

DIAGNOSTIC ISSUES (CONT'D)

THROMBOPHILIA WORKUP—should be done if suspect a hereditary cause of thromboembolic disease. Alarm features include age < 45, unprovoked VTE family history (1 or more first degree relatives), or clot in unusual location (mesenteric vessels, brain)

MALIGNANCY WORKUP—basic screening includes history and physical, CXR, CBC, LFTs, calcium, and U/A. Consider CT abdomen and pelvis for those >40 years. Consider mammography for women >40 years

PROTEIN S AND PROTEIN C DEFICIENCY WHILE ANTICOAGULATED—when anti-coagulated, these levels decrease by similar proportion to II, VII, IX and X

MANAGEMENT

ANTICOAGULATION—see Approach to Anticoagulation Table

IVC FILTER—if anticoagulation contraindicated

THROMBOLYSIS—may have a role in hemodynamically unstable pulmonary embolism (systemic) or massive iliofemoral thrombosis (local)

TREATMENT ISSUES

ANTICOAGULATION DURATION

- **3–6 MONTHS**—first DVT with reversible or time-limited risk factor removed (i.e. if DVT in second term of pregnancy, stop therapy 3 months post-partum)
- **AT LEAST 1 YEAR**—idiopathic VTE
- **LIKELY LIFELONG**—recurrent idiopathic DVT or continuing major risk factor (malignancy, antithrombin III deficiency, homozygous factor V Leiden, homozygous prothrombin G20210A, heterozygous factor V Leiden plus prothrombin G20210A)

CONTRAINDICATIONS TO ANTICOAGULATION THERAPY

- **ABSOLUTE**—neurosurgery, ocular surgery, or intracranial bleeding within the past 10 days, active bleeding, severe bleeding diathesis
- **RELATIVE**—mild–moderate bleeding diathesis or thrombocytopenia ($<25 \times 10^3/\mu L$), brain metastases from melanoma, renal cell carcinoma, choriocarcinoma and thyroid cancers, recent major trauma, major abdominal surgery < 2 days, GI or GU bleeding < 2 weeks, endocarditis, severe hypertension (>200/120 mmHg)

TREATMENT ISSUES (CONT'D)

SPECIFIC ENTITIES

SUPERFICIAL THROMBOPHLEBITIS—characterized by painful, erythematous, palpable cord along a superficial vein usually in the lower extremity, can be associated with hypercoagulable states. 25% will have synchronous ipsilateral DVT and a new DVT develops within 3 months in 10%

CATHETER RELATED THROMBOSIS

- **INCIDENCE**—approximately 40% (range 12-74%) of patients with long term central venous catheter develop DVT
- **RISK FACTORS**—in addition to traditional risk factors (e.g. cancer), left subclavian vein placement, positioning of catheter tip too high in the superior vena cava and previous catheter infections
- **CLINICAL FEATURES**—often asymptomatic. However, patients may experience arm swelling, erythema, pain, warmth, development of collateral vessels and fever. Acute PE, post thrombotic syndrome and persistent vascular compromise represent potential complications
- **DIAGNOSIS**—ultrasound (sens 78-100%, spc 86-100%), venogram is gold standard but rarely done
- **TREATMENTS**—if catheter is still needed (e.g. for chemotherapy administration), consider anticoagulation for at least 3 months with catheter in place, followed by prophylactic doses until catheter removed. Note that in serious cases in which the limb may be threatened or if anticoagulation is contraindicated, catheter may need to be removed regardless. If no need for catheter, consider anticoagulation for 3–5 days, then remove catheter, and then anticoagulation for up to 3 months. Primary prophylaxis is not indicated

Approach to Anticoagulation Therapies

Class/Drugs	Mechanism	Indications	Usual dose	Complications/monitoring
Warfarin	Inhibition of gamma carboxylation by inhibition of the vitamin K-dependent epoxide reductase. Inhibits hepatic synthesis of vitamin K-dependent factors (II, VII, IX, X, protein S, protein C)	DVT/PE Atrial fibrillation Prosthetic valves	*Warfarin* 5 mg PO daily overlapping with heparin for 5 days, then adjust based on INR target of 2–3	**Complications**—bleeding (may be reversed with vitamin K), coumadin-induced skin necrosis **Monitor**—INR
Unfractionated heparin	**Indirect thrombin and factor Xa inhibitor** (**nonselective**). Binds to antithrombin (AT) and converts it from a slow form to fast-acting form, which binds and inactivates thrombin and factors Xa, IXa, XIa, XIIa Heparin resistance is usually due to AT deficiency and could be treated with AT concentrates	Acute DVT/PE Arterial embolism Prosthetic valves ACS DVT prophylaxis	For acute clot, *unfractionated heparin* 80 U/kg or 5,000 U IV bolus, then 18 U/kg/h or 1,000 U/h, and adjust to 1.5–2.5× normal PTT For DVT prophylaxis, *unfractionated heparin* 5,000U SC 2 h before surgery, then 5,000U SC TID	**Complications**—bleeding (may be reversed by protamine 1 mg/100 U UFH), HITT, osteoporosis **Monitor**—aPTT (1.5–2.5× normal) and platelets Narrow therapeutic window and highly variable dose–response curve
Low molecular weight heparin: *Enoxaparin* *Dalteparin* *Tinzaparin*	**Indirect factor Xa inhibitor** (**relatively selective**). Binds to AT and converts it from a slow form to fast acting form, which binds and inactivates factor Xa, and to a smaller extent, thrombin Inactivation of thrombin specifically requires heparin binding to *both* AT and thrombin. This complex only forms with heparin chains ≥18-saccharide long. Thus, LMWH is not as effective in inhibiting thrombin and does not prolong aPTT	Acute DVT/PE Maintenance DVT/PE in cancer patients Arterial embolism Prosthetic valves ACS DVT prophylaxis	For acute clots, *enoxaparin* 1 mg/kg SC BID or 1.5 mg/kg SC daily, *dalteparin* 200 U/kg SC daily, tinzaparin 175 U/kg SC daily For DVT prophylaxis, *enoxaparin* 40 mg SC daily × 7–14 days starting 12 h pre-op, *dalteparin* 2500 U SC 1 h pre-op, then 5000 U SC daily × 5–14 days	**Complications**—bleeding (may be reversed partially with protamine sulfate 1 mg/100 anti-Xa U of LMWH), HITT, avoid in spinal surgery **Monitor**—anti-factor Xa activity and platelets. Anticoagulant response correlates well with body weight, allowing fixed dosing without monitoring usually. Less likely to induce HITT but still requires platelet monitoring

Approach to Anticoagulation Therapies (cont'd)

Class/Drugs	Mechanism	Indications	Usual dose	Complications/monitoring
Heparinoids: *Danaparoid* (*organon*)	**Indirect factor Xa inhibitors** (**selective**). Mixture of heparin sulfate, dermatan sulfate, and chondroitin sulfate. Inhibits thrombin via a combination of AT (heparin cofactor I), heparin cofactor II, and some undefined mechanism. aPTT not useful for monitoring	HITT Acute DVT	For HITT, *danaparoid* 2,000 anti-factor Xa U IV bolus, then 150–200 U/h, titrate to plasma anti-Xa level of 0.5–0.8 U/mL	**Complications**—bleeding **Monitor**—anti-factor Xa activity. Particularly important in renal failure 10% cross-reactivity between danaparoid and the antibody responsible for HITT, but clinical significance is uncertain
Fondaparinux	**Indirect factor Xa inhibitor** (**highly selective**). Similar to LMWH, but only a pentasaccharide that binds strongly to AT and inactivates factor Xa. Complex does not bind thrombin due to short length	DVT prophylaxis Acute DVT/PE Acute coronary syndrome HITT (no cross reactivity with heparin-dependent anti-platelet antibodies)	For DVT prophylaxis, *fondaparinux* 2.5 mg SC daily (start 6–8 h after surgical hemostasis) For acute clots, *fondaparinux* 5 mg SC daily for weight <50 kg, 7.5 mg SC daily for weight 50–100 kg, 10 mg SC daily for weight >100 kg	**Complications**—bleeding; avoid in spinal surgery **Monitor**—antifactor Xa activity
Oral Direct Factor Xa inhibitor: *Rivaroxaban*[a] *Apixaban*[a]	**Direct factor Xa inhibitors** (**highly selective**). Inhibits factor Xa by binding to its active site without interacting with AT	DVT prophylaxis VTE treatment (except if hemodynamically unstable or massive PE) Atrial fibrillation	For DVT prophylaxis, *rivaroxiban* 10 mg PO daily or *apixaban* 2.5 mg PO BID For acute VTE, *rivaroxaban* 15 mg PO BID for 3 weeks, *apixaban* 10 mg PO BID for 7 days For atrial fibrillation, *rivaroxaban* 20 mg PO daily or *apixaban* 5 mg PO BID	**Complications**—bleeding **Monitor**—no routine monitoring assay is available
Direct thrombin inhibitors: *Desirudin* *Bivalirudin* *Argatroban* *Dabigatran*[a]	**Direct thrombin inhibitors** (**highly selective**). AT independent. In contrast to heparin, LMWH, and heparinoid, direct thrombin inhibitors can inhibit clot-bound thrombin because their sites for binding (active site ± exosite I) are not masked by fibrin. Does not depend on AT for action and thus unaffected by AT deficiency	HITT (argatroban, bivalirudin) ACS (bivalirudin) DVT prophylaxis (desirudin) VTE treatment (dabigatran) Atrial fibrillation (dabigatran)	For HITT, *argatroban* 2 μg/kg/min infusion For DVT prophylaxis, *desirudin* 15 mg SC BID For VTE treatment, *dabigatran* 150 mg PO BID after 5 days heparin For atrial fibrillation, *dabigatran* 150 mg PO BID	**Complications**—bleeding **Monitor**—aPTT is unreliable **Dose adjust dabigatran**—ClCr < 30 ml/min

[a]Novel oral anticoagulants

Related Topics
DVT (p. 176)
Hypercoagulable States (p. 173)
Pulmonary Embolism (p. 10)

WARFARIN-INDUCED SKIN NECROSIS

CLINICAL FEATURES—usually within first few days of warfarin therapy (especially large loading doses) → significantly decreases protein C levels → transient hypercoagulable → erythematous macule → purpuric zone → necrotic lesion. Occurs over extremities, breast, trunk, and penis

TREATMENTS—immediately stop warfarin, give vitamin K, heparin IV, consider FFP or protein C concentrate. Lesion may continue to progress despite adequate anticoagulation

CORRECTION OF SUPRATHERAPEUTIC INR DUE TO WARFARIN USE

INR < 5—if no significant bleeding, rapid reversal is not indicated. Reduce warfarin dose or hold the next warfarin dose

CORRECTION OF SUPRATHERAPEUTIC INR DUE TO WARFARIN USE (CONT'D)

INR 5–9—if no significant bleeding, hold the next 1–2 doses of warfarin or omit the next dose of warfarin ± administer *vitamin K1* 2.5 mg PO. If rapid reversal required (e.g. bleeding or urgent surgery), *FFP* 10–20 mL/kg + *vitamin K1* 2–4 mg PO (↓ INR within 24 h), if INR remains high at 24 h, give additional *vitamin K1* 1–2 mg PO. May also consider prothrombin complex concentrate in selected cases

INR > 9—if no significant bleeding, hold warfarin and administer *vitamin K1* 2.5–5 mg PO. Use additional vitamin K1 if indicated by frequent INR monitoring. If serious bleeding, hold warfarin, administer *FFP* 20–30 mL/kg + *vitamin K1* 10 mg by slow IV infusion. Also can use prothrombin complex concentrate or recombinant factor VIIa, depending on volume status and urgency. If life-threatening bleeding, hold warfarin therapy and administer recombinant factor VIIa, FFP, and *vitamin K1* 10 mg by slow IV infusion. Monitor INR and repeat as necessary. May also consider prothrombin complex concentrate in selected cases

Transfusion Reactions

COMPLICATIONS OF TRANSFUSIONS

Adverse Effect	Pathophysiology	Onset and Symptoms	Treatments
ABO incompatibility	Recipient Ab against donor RBC major antigen, 1/40,000	Immediate. Fever, ↓ BP, CP, lumbar pain, hemoglobinuria, and bleed	Stop transfusion and check blood. Fluids, diuretics, FFP, dialysis
Acute hemolytic reaction	Recipient Ab against donor RBC minor antigen, 1/600,000	Acute/delay. Milder form of above	Stop transfusion and check blood. Fluids, diuretics, FFP, dialysis
Febrile reaction	Recipient Ab against donor WBC PRBC, 1/300; or platelets (5U), 1/10	End of transfusion. Fever, chills	Antihistamine (*diphenhydramine* 50 mg IV × 1 dose), acetaminophen
Anaphylaxis	Recipient Ab against donor IgA, 1/40,000	Immediate. ↓ BP, bronchospasm, no fever	Stop transfusion, epinephrine, corticosteroids
Urticaria	Recipient IgE against donor antigens, 1/100 plasma-containing products	Acute. Pruritic rash	Antihistamine (*diphenhydramine* 50 mg IV × 1 dose)

Transfusion Reactions (cont'd)

Adverse Effect	Pathophysiology	Onset and Symptoms	Treatments
Post-transfusion purpura (PTP)	Recipient Ab against donor platelet, rare	7–10 days after. Consumptive thrombocytopenia and purpura	Steroids, plasmapheresis
Transfusion-associated circulatory overload (TACO)	Hypervolemia 1/700	Acute/delay. Pulmonary edema	Diuresis, supportive measures
Septic transfusion	Platelets (5 U) 1/10,000 risk of symptomatic sepsis and 1/40,000 chance of death PRBC (1 U), 1/100,000 risk of symptomatic sepsis and 1/500,000 chance of death	Acute. Fever, ↓ BP	Stop transfusion, empiric antibiotics (vancomycin + broad spectrum beta-lactam or aminoglycoside)
Air embolism		Acute. SOB, ↓ BP	Supportive measures
TRALI	Donor Ab against recipient WBC, 1/5,000 plasma-containing products	Acute. Hypoxemic, pulmonary edema	Supportive measures
GVHD	Donor lymphocytes against recipient tissue	Delay. Rash, hepatitis, diarrhea	
Infection risk	HIV 1/10 million, HCV 1/3 million, HBV 1/72,000, HTLV1 1/2 million, West Nile virus < 1/1 million		

INVESTIGATIONS

BLOOD TESTS—CBCD, peripheral smear, urea, Cr, LDH, indirect bilirubin, serum hemoglobin, Coombs testing, PTT, INR, fibrinogen, blood C&S, send blood product for culture/typing
URINE TESTS—urinalysis
IMAGING—CXR

INDICATIONS FOR SPECIALLY PREPARED BLOOD PRODUCTS

WASHED TRANSFUSION PRODUCT (removes almost all serum proteins and most leukocytes)—IgA deficiency, previous anaphylactic transfusion reaction, febrile reactions not prevented by leukocyte reduction, severe urticarial reactions not prevented by the antihistamines
LEUKOCYTE-DEPLETED TRANSFUSION PRODUCT (removes most leukocytes)—prevention of febrile reactions or TRALI, prevention of HLA alloimmunization (leukemia, aplastic anemia, chronic hemolytic anemia, MDS, MPS), transplant candidates, substitute for CMV-negative blood
IRRADIATED TRANSFUSION PRODUCTS (inhibits lymphocyte proliferation and prevents transfusion-associated GVHD)—stem cell transplant recipients, recipients of directed donor transfusions from blood relatives, Hodgkin's lymphoma
CMV-NEGATIVE TRANSFUSION PRODUCTS (screened)—CMV-negative transplant recipients (solid organ or bone marrow from CMV negative donors), antepartum transfusions for CMV-negative women

Approach to the Peripheral Blood Smear

TERMS

ANISOCYTOSIS—varying sizes of RBC
POIKILOCYTOSIS—varying shapes of RBC
HYPOCHROMIA—present when the central pale area >1/3 diameter. Occurs in iron deficiency, thalassemia, and lead poisoning

RBC INTRACELLULAR INCLUSIONS

BASOPHILIC STIPPLING—β-thalassemia, lead, or arsenic poisoning
HEINZ BODIES—G6PD deficiency, alpha thalassemia
PAPPENHEIMER BODIES—non-nucleated RBC containing such inclusions are called siderocytes, due to hyposplenism, thalassemia, and sideroblastic disorders. Nucleated RBC are termed sideroblasts
NUCLEATED RBC—acute systemic hypoxia, intense erythropoietin stimulation, infiltrative narrow processes, extramedullary erythropoiesis
HOWELL–JOLLY BODIES—asplenia, megaloblastic hematopoiesis
POLYCHROMASIA—RBC with diffuse bluish discoloration due to the presence of RNA. Increased number of cells showing polychromasia indicates reticulocytosis

TELLTALE MORPHOLOGIES

TARGET CELLS—liver disease (especially obstructive jaundice, hepatitis), thalassemia, post-splenectomy, hemoglobinopathies (hemoglobin C and E), lecithin–cholesterol acyltransferase deficiency
FRAGMENTED CELLS (schistocytes, helmet cells)—microangiopathic hemolytic anemia (DIC, TTP, HUS), aortic valve prosthesis
TEAR DROP CELLS (dacrocytes)—myelophthisis, myelofibrosis with myeloid metaplasia (MMM), severe iron deficiency, thalassemia major. Disappear after splenectomy
BURR CELLS (echinocytes)—uremia, artifact
SPUR CELLS (acanthocytes)—chronic liver disease, abetalipoproteinemia, malabsorption, anorexia nervosa
SPHEROCYTES—due to loss of membrane surface area. Associated with autoimmune hemolytic anemia (microspherocytes), hereditary spherocytosis, and *Clostridium* infections
ELLIPTOCYTOSIS (ovalocytosis)—hereditary elliptocytosis, megaloblastosis
STOMATOCYTES—acute alcoholism, chronic liver disease, artifact
ROULEAUX—stacking of RBC suggestive of high ESR or hypergammaglobulinemia. Causes include malignancies (myeloma), infections, and connective tissue disease

Splenomegaly

DIFFERENTIAL DIAGNOSIS

CONGESTIVE—right heart failure, constrictive pericarditis, tricuspid regurgitation, IVC obstruction, hepatic/splenic vein obstruction, cirrhosis with portal hypertension
INFILTRATIVE

- **MALIGNANCY**—lymphoma (Hodgkin's, non-Hodgkin's, hairy cell leukemia), leukemia (CLL, CML), myeloproliferative disorders (PRV, CML, ET, MF), splenic tumor, metastasis
- **AMYLOIDOSIS**
- **SARCOIDOSIS**
- **CONGENITAL STORAGE DISEASES**—Gaucher, Niemann-Pick disease

REACTIVE

- **INFECTIONS**—**bacterial** (endocarditis, sepsis, TB, MAC), **viral** (mononucleosis, hepatitis), **fungal** (*Histoplasma*), **parasitic** (malaria, *Leishmania*, trypanosomiasis)
- **INFLAMMATORY**—rheumatoid arthritis (Felty's syndrome), SLE, Still's disease
- **SICKLE CELL, HEMOGLOBIN C, THALASSEMIA, IgG-MEDIATED AUTOIMMUNE HEMOLYTIC ANEMIA**

CLINICAL FEATURES

SIX WAYS TO DISTINGUISH SPLEEN FROM LEFT KIDNEY

1. Spleen has no palpable upper border
2. Spleen has a notch
3. Spleen moves inferomedially on inspiration while the kidney moves inferiorly

CLINICAL FEATURES (CONT'D)

4. Spleen is not usually ballotable unless gross ascites are present, but the kidney is because of its retroperitoneal position
5. The percussion note is dull over the spleen but is usually resonant over the kidney

CLINICAL FEATURES (CONT'D)

6. A friction rub may occasionally be heard over the spleen, but never over the kidney because it is too posterior

RATIONAL CLINICAL EXAMINATION SERIES DOES THIS PATIENT HAVE SPLENOMEGALY?

NORMAL SPLEEN—<250 g [<0.55 lb] or 250 cm^3, 12 cm by 7 cm [4.7 in. by 2.8 in.]. anatomically, the spleen lies below the left diaphragm. It follows the curvature of left 10th rib and points anteriorly toward, the left colic flexure

	LR+	LR–
Percussion		
Nixon's method (right lateral decubitus position; percuss from lower level of pulmonary resonance in posterior axillary line downward obliquely to lower mid-anterior costal margin; >8 cm suggests splenomegaly)	3.6	0.41
Traube's space (percuss space 6th rib superiorly, mid-axillary line laterally and costal margin inferiorly; dullness suggests splenomegaly	2.3	0.48
Castell's method (percuss lowest intercostal space in the left anterior axillary line during both expiration and full inspiration; dullness suggests splenomegaly	1.2	0.45
Palpation		
One-handed palpation with patient supine	8.2	0.41
Middleton hooking maneuver	6.5	0.16

APPROACH—"given the low sensitivity of the clinical examination, routine examination for splenomegaly cannot definitively rule in or rule out splenomegaly in normal, asymptomatic patients where the prevalence is <10% and additional imaging tests will be required. Rather, the examination for splenomegaly is most useful to rule in the diagnosis of splenomegaly among patients in whom there is a clinical suspicion of at least 10%. The examination should always start with percussion. If no dullness is detected on percussion, there is no need to palpate as the results of palpation will not effectively rule in or rule out splenic enlargement. If the possibility of missing splenic enlargement remains an important clinical concern, then ultrasound or scintigraphy is indicated. In the presence of percussion dullness, palpation should follow. If both tests are positive, the diagnosis of splenomegaly is established (providing the clinical suspicion of splenomegaly was at least 10% before examination). If palpation is negative, diagnostic imaging will be required to confidently rule in or rule out splenomegaly"

JAMA 1993 270:18

UPDATE—palpation may have greater accuracy than percussion, especially in lean patients. Examiners should become proficient in one palpation and one percussion method, because the combination of both results may be better than either alone.

The Rational Clinical Examination. McGraw-Hill, 2009

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, AST, ALT, ALP, bili
- **MICROBIOLOGY**—blood C&S
- **IMAGING**—US abd

SPECIAL

- **CT ABD**—weight = 0.43 × Length × Width × Thickness
- **SCINTIGRAPHY**
- **MALIGNANCY WORKUP**—bone marrow biopsy, lymph node biopsy, laparoscopy/laparotomy

MANAGEMENT

TREAT UNDERLYING CAUSE

SPLENECTOMY—see p. 163 for more details

SPECIFIC ENTITIES

CAUSES OF MASSIVE SPLENOMEGALY—lymphoma, hairy cell leukemia, CML, myelofibrosis, malaria, MAC in HIV, thalassemia major, sarcoidosis, Gaucher's disease

Myeloproliferative Disorders

NEJM 2007 357:3

DIFFERENTIAL DIAGNOSIS

ESSENTIAL THROMBOCYTOSIS (ET)
POLYCYTHEMIA RUBRA VERA (PRV)
CHRONIC MYELOGENOUS LEUKEMIA (CML)
MYELOFIBROSIS (MF)
OTHERS—chronic eosinophilic leukemia, chronic myelomonocytic leukemia (CMML), chronic neutrophilic leukemia, systemic mastocytosis

PATHOPHYSIOLOGY

MYELOPROLIFERATIVE DISORDERS—associated with increased red blood cells (especially PRV), white blood cells (especially CML), and/or platelets (especially ET). MPS should not be confused with myelodysplastic syndrome (MDS), which is associated with a decreased production of dysplastic blood cells. Both MPS and MDS can eventually lead to AML

POLYCYTHEMIA RUBRA VERA—see POLYCYTHEMIA (p. 159)

CHRONIC MYELOGENOUS LEUKEMIA (CML)—a stem cell disease with Philadelphia chromosome t(9;22) leading to fusion gene *bcr–abl*, found in erythroblasts, megakaryocytes, granulocytes, monocytes, and most lymphocytes. ↓ LAP. Chronic phase → accelerated phase → blast crisis, 2/3 myeloid, 1/3 lymphoid

- **CHRONIC PHASE** (5–6 years)— < 15% blasts, <20% basophils, and <30% blasts plus promyelocytes
- **ACCELERATED PHASE** (6–9 months)—15–29% blasts, ≥20% basophils, ≥30% blasts + promyelocytes or platelets $<100\times10^3/\mu L$
- **BLAST CRISIS** (3–6 months)— ≥ 30% blasts or extramedullary involvement (chloroma). Usually constitutional symptoms, worsening blood counts, and may have extra Ph chromosome, inv(17q), trisomy 8, and trisomy 19

CHRONIC MYELOMONOCYTIC LEUKEMIA (CMML)—also known as smoldering leukemia, with persistent unexplained monocytosis. Classified as "MDS/MPS." Clinical features include leukocytosis (monocytosis $>1.0\times10^3/\mu L$ for at least 6 months), anemia, thrombocytopenia, and splenomegaly

ESSENTIAL THROMBOCYTOSIS—see THROMBOCYTOSIS (p. 166)

MYELOFIBROSIS—↑ fibroblasts, massive spleen, teardrop RBC, nucleated RBC, large platelets

Related Topics
Polycythemia (p. 159)
Thrombocytosis (p. 166)

CLINICAL FEATURES

HISTORY—B symptoms (fever, night sweats, weight loss, pruritus), hyperviscosity symptoms (facial plethora, headache, visual or mental status changes, stroke, or another ischemic/thrombotic event)

PHYSICAL—splenomegaly

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, reticulocyte count, uric acid
- **BONE MARROW BIOPSY**—not useful for PRV. Consider cytogenetic studies of blood/bone marrow (FISH) or quantitative PCR to look for Ph chromosome

SPECIAL

- **GENETIC TESTING**—JAK2 mutation (sensitivity ~100% for PRV and highly specific for other myeloproliferative disorders), *bcr–abl* testing (CML)
- **LEUKOCYTE ALKALINE PHOSPHATASE** (LAP)—↑ in PRV, MF, ET, and leukemoid reactions; can be ↓ in CML and CMML
- **VITAMIN B12**—↑ in CML due to granulocyte transcobalamin I levels
- **EPO**—↓ in PRV

DIAGNOSTIC AND PROGNOSTIC ISSUES

LEUKOCYTE ALKALINE PHOSPHATASE—elevated in PRV, MF, and ET, but decreased in CML and CMML

POLYCYTHEMIA RUBRA VERA—median survival 20 years; ~14/100 transform to AML over 2 decades

CHRONIC MYELOGENOUS LEUKEMIA—median survival is now decades and risk of blast crisis is declining with *bcr-abl* tyrosine kinase inhibitors; ~1/2 transforms to AML

ESSENTIAL THROMBOCYTOSIS—median survival 20 years; ~25/1,000 transform to AML over 3 decades

MYELOFIBROSIS—median survival 5 years; ~1/10 transforms to AML

MANAGEMENT

POLYCYTHEMIA RUBRA VERA—phlebotomy 1–2/week, aspirin, hydroxyurea

CHRONIC MYELOGENOUS LEUKEMIA

- **CHRONIC PHASE**—*imatinib mesylate* 400–800 mg PO daily with cytogenetic response rate 63%, dasatinib and nilotinib may be used

MANAGEMENT (CONT'D)

for imatinib resistant disease. Allogeneic stem cell transplant is associated with 60–70% cure rate

- **ACCELERATED PHASE**—*imatinib mesylate* 600–800 mg PO daily. Allogeneic stem cell transplant is associated with 30–45% cure rate
- **BLAST CRISIS**—*imatinib mesylate* 800 mg PO daily, plasmapheresis. Allogeneic stem cell transplant is associated with 10–15% cure rate
- **IMATINIB-RESISTANT CML**—dasitinib, nilotinib, and stem cell transplantation

ESSENTIAL THROMBOCYTOSIS—aspirin, hydroxyurea, anagrelide

MYELOFIBROSIS—hydroxyurea, ruxolitinib, splenectomy, interferon α, thalidomide

TREATMENT ISSUES

RESPONSE CRITERIA FOR CML

- **HEMATOLOGICAL RESPONSE**
  - **COMPLETE RESPONSE**—WBC $<10\times10^3/\mu L$ with no immature granulocytes and <5% basophils, platelet $<450\times10^3/\mu L$, and non-palpable spleen
  - **PARTIAL RESPONSE**—persistence of immature cells in peripheral blood, platelets $>450\times10^3/\mu L$ but <50% of pre-treatment levels, or persistent splenomegaly but <50% of pre-treatment size
- **CYTOGENIC RESPONSE** (FISH detection of the Philadelphia chromosome)
  - **COMPLETE**—0% Ph + cells
  - **PARTIAL**—1–35% Ph + cells
  - **MAJOR**—complete and partial cytogenetic response

TREATMENT ISSUES (CONT'D)

  - **MINOR**—36–65% Ph + cells
  - **MINIMAL**—66–95% Ph + cells
- **MOLECULAR RESPONSE** (bcr–abl transcript detection by RT-PCR)
  - **COMPLETE**—negative
  - **MAJOR**—bcr–abl to control gene ratio <0.1 (3 log decrease in bcr–abl transcript in peripheral blood) where HR = hematologic response, CHR = complete hematologic response, CGR = cytogenetic response, PCGR = partial cytogenetic response, CCGR = complete cytogenetic response, MMR = major molecular response, ACA = additional chromosomal abnormality

MONITORING FOR CHRONIC MYELOGENOUS LEUKEMIA—bone marrow annually, quantitative PCR every 3 months (repeat test in 4 weeks if >0.5 log increase)

IMATINIB RESISTANCE—*bcr–abl* mutations (T315I mutation confers tyrosine kinase inhibitor resistance), overexpression or amplification of *bcr–abl*

DEFINITION OF TREATMENT FAILURE FOR CML PATIENTS ON IMATINIB THERAPY

Months	Suboptimal	Failure
3	<CHR	No HR
6	<PCGR	<CHR, no CGR
12	<CCGR	<PCGR
18	<MMR	<CCGR
Anytime	ACA, loss of MMR	Loss of CHR or CCGR

Acute Myelogenous Leukemia NEJM 1999 341:14

HEMATOLOGIC MALIGNANCIES OVERVIEW

MYELO—bone marrow. Myeloproliferative disorders (PRV, CML, ET, and MF) involve cell accumulation, while myelodysplastic disorders involve abnormal bone marrow cell growth. Both disorders have risk of transformation to acute myeloid leukemia

MYELOID—neutrophils, monocytes, macrophages, eosinophils, basophils, mast cells, erythrocytes, platelets, and their precursors. Myeloid malignancies include AML and CML

LYMPHOID—B cells, T cells, natural killer cells. Lymphoid malignancies include ALL, CLL, and all lymphomas

HEMATOLOGIC MALIGNANCIES OVERVIEW (CONT'D)

LEUKEMIA—malignant cells in blood and/or bone marrow. May be myeloid (AML, CML) or lymphoid* (LL/ALL, SLL/CLL) in origin. Myeloid leukemia seldom presents in lymph nodes

- **ACUTE LEUKEMIA**—involves immature blast cells. More aggressive course
- **CHRONIC LEUKEMIA**—involves mature differentiated cells. More indolent course

LYMPHOMA—malignancy of lymphoid origin and presents more in lymphoid organs

- **HODGKIN'S LYMPHOMA**—B cell (Reed–Sternberg cell)

HEMATOLOGIC MALIGNANCIES OVERVIEW (CONT'D)

- **NON-HODGKIN'S LYMPHOMA**—B, T, or NK cells

*lymphoblastic lymphoma (LL) = acute lymphoblastic leukemia (ALL). Small lymphocytic lymphoma (SLL) = chronic lymphocytic leukemia (CLL)

PATHOPHYSIOLOGY OF AML

EPIDEMIOLOGY

- **INCIDENCE**—1–2% of all cancers, 90% of all acute leukemias in adulthood, mean age 65
- **MORTALITY**—1.5% of all cancers

RISK FACTORS

- **FAMILY HISTORY**—family history (3×), Down's, Klinefelter, Fanconi syndrome, Bloom's, ataxia telangiectasia, neurofibromatosis
- **ENVIRONMENTAL**—previous chemotherapy (alkylating agents [melphalan, cyclophosphamide, chlorambucil, temozolomide], topoisomerase II inhibitors [anthracyclines, etoposide]), radiation, benzene
- **DISEASES**—MDS, MPS (PRV, CML, ET, MF), PNH, aplastic anemia

DISTINGUISHING FEATURES BETWEEN TREATMENT-INDUCED AMLs

	Alkylating agents	Topoisomerase II inhibitors
Latency	5–7 years	2–3 years
MDS pre-AML	Yes	No
AML types	All, M1–2	M4–5
Karyotype	–5, –7	11q23, 21q22, inv16
Prognosis	Worse	Poor except for Inv16 karyotype

CLINICAL FEATURES

PANCYTOPENIA—weakness, fatigue, infections, gingival bleed, ecchymosis, epistaxis, menorrhagia

BONE PAIN—ribs, sternum, long bones

CUTANEOUS LESIONS—leukemic cutis (especially M4, M5), chloromas (skin local collection of blasts, granulocytic sarcoma especially M2), gum hypertrophy (M5)

CNS LEUKEMIA (especially M4, M4EO, and M5)

DIC—associated with M3 subtype

NOTE: lymphadenopathy, hepatosplenomegaly not common

INVESTIGATIONS

BASIC

- **LABS**—CBCD, smear (Auer rods), lytes, urea, Cr, Ca, PO_4, Mg, uric acid, albumin, urinalysis, LDH, INR, PTT, fibrinogen
- **BONE MARROW BIOPSY** (>**20**% **BLASTS**) **WITH FLOW CYTOMETRY AND CYTOGENETIC/MOLECULAR ANALYSES**

SPECIAL

- **LUMBAR PUNCTURE**—CSF for cytology (risk of CNS involvement greatest with high circulating blasts, elevated LDH, and monocytic variants of AML) and flow cytometry
- **HLA TESTING**—to assist in obtaining HLA-matched platelets if needed during treatment and to find HLA-matched allogeneic bone marrow

DIAGNOSTIC AND PROGNOSTIC ISSUES

DIAGNOSTIC CRITERIA—>20% blasts in bone marrow

HISTOLOGIC TYPE

- **FAB M0**—AML, minimally differentiated
- **FAB M1**—AML, without maturation (19%)
- **FAB M2**—AML, with maturation (32%)
- **FAB M3**—acute promyelocytic leukemia (PML), with both hypergranular and variant microgranular subtypes (M3v)
- **FAB M4**—acute myelomonocytic leukemia (AMML), including the variant AMML with abnormal eosinophils (M4EO) (17%)
- **FAB M5**—acute monoblastic leukemia, including poorly differentiated (M5a) and differentiated (M5b)
- **FAB M6**—acute erythroleukemia
- **FAB M7**—acute megakaryoblastic leukemia

PROGNOSTIC FACTORS

- **GOOD RISK** (70% 5-year survival, 33% relapse)—favorable karyotypes t(8;21), t(15;17), inv(16)/t(16;16)/del(16q), FAB M3
- **INTERMEDIATE RISK** (48% 5 year survival, 50% relapse)—neither good nor bad; normal cytogenetics or trisomy 8
- **POOR RISK** (15% 5-year survival, 78% relapse)—adverse karyotypes include monosomy chromosome 5 or chromosome 7, del(5q), abn(3q26), t(6;9), 11q23 aberrations except for t(9;11), or multiple chromosomal changes, resistant disease after first course of chemotherapy (>15% blasts)
- **ADDITIONAL POOR PROGNOSTIC FACTORS**—age >60, Karnofsky score <60%, CD34+, MDR1+, FLT3 mutation, prior MDS, MPS, chemotherapy, radiation, t(6;9), LDH >2.9 × ULN

MANAGEMENT

AGE < 60

- **INDUCTION CHEMOTHERAPY**—IDAC (also known as the 7 + 3 regimen, cytarabine × 7 days + one of daunorubicin/idarubicin/mitoxantrone × 3 days), HDAC (same except higher dose of cytarabine q12h × 12 doses leads to longer disease free survival) or NOVE (mitoxantrone plus etoposide)
- **CONSOLIDATION TREATMENT**
  - **COMPLETE REMISSION POST-INDUCTION**
    - **GOOD RISK**—chemotherapy IDAC induction followed by HDAC consolidation
    - **INTERMEDIATE RISK**—stem cell transplant (SCT) if available; otherwise, consolidation chemotherapy
    - **POOR RISK**—SCT if donor available; otherwise, consolidation chemotherapy
  - **LACK OF COMPLETE REMISSION POST-INDUCTION**—repeat induction. Proceed as in poor risk disease
- **RELAPSE**—SCT if donor available (preferred); otherwise, salvage chemotherapy

AGE > 60—individualized treatment. If unable to tolerate aggressive therapy, consider IDAC with attenuated doses or palliation with hydroxyurea cytoreduction

Related Topics
Febrile Neutropenia (p. 263)
Tumor Lysis Syndrome (p. 254)

TREATMENT ISSUES

COMPLETE REMISSION—normal BM cellularity, <5% blasts in BM, none with leukemic phenotype or abnormal cytogenetics. Lumbar puncture after complete remission with induction chemotherapy, especially those with monoblastic phenotype. After induction, the remission rate in younger patients (<55 years) is 70–85%, but only 40–50% in older patients

SCT—may opt for consolidation chemotherapy while identifying donor. SCT is a potentially curative therapy

SPECIFIC ENTITIES

MYELODYSPLASTIC SYNDROME (MDS)—opposite of myeloproliferative disorders, decreased cell counts

- **SUBTYPES**—refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with multilineage dysplasia, refractory anemia with multilineage dysplasia and ringed sideroblasts, refractory anemia with excess blasts (RAEB) 5–10% blasts, refractory anemia with excess blasts in transformation (RAEB-t) 10–19% blasts, MDS unclassified. RA and RARS are at low risk of transforming to AML (i.e. >20% blasts), while the rest are at high risk
- **DIAGNOSIS**—peripheral blood smear (RBC with abnormal morphologic features, dysgranulopoiesis with Pelger-Huët deformity, nuclear atypia and hypogranulation, monocytosis), bone marrow biopsy

INTERNATIONAL PROGNOSTIC SCORING SYSTEM FOR MYELODYSPLASTIC SYNDROMES

Score	0	0.5	1	1.5	2
% blasts in BM	<5	5–10	–	11–20	21–30
Karyotype	Good	Med.	Poor	–	–
Cytopenia	0/1	2/3	–	–	–

For karyotype, good = –y, del(5q), del(20q); medium = neither good nor poor; poor = chromosome 7 or complex abnormalities

Risk group	Score	Median survival
Low	0	5.7 years
Intermediate 1	0.5–1.0	3.5 years
Intermediate 2	1.5–2.0	1.2 years
High	≥2.5	0.4 year

- **TREATMENTS**—transfusions, erythropoietin/darbopoietin (for patients with serum EPO <500 ng/ml and low transfusion requirement), treat infections early, 5-azacytidine, lenalidomide, decitabine, stem cell transplant (IPSS ≥1.5)

ACUTE PROMYELOCYTIC LEUKEMIA (M3, APL, PML)

- **PATHOPHYSIOLOGY**—associated with t(15;17)(q22;q21), which results in fusion of PML gene and retinoic acid receptor α gene. This gene product plays a key role in leukemogenesis. Other combinations include t(11;17) with fusion of PLZF gene, t(5;17) with fusion of NPM gene, or t(11;17) with fusion of NuMA gene. Note that all except PLZF-RARA are susceptible to retinoic acid treatment
- **CLINICAL FEATURES**—similar to AML. DIC commonly occurs in PML and should be monitored closely

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—**induction** with all-*trans*-retinoic acid (ATRA) plus idarubicin, then **consolidation** with anthracycline and cytarabine, and then **maintenance** with ATRA for 1 year. Retinoic acid exerts its effect via (1) degradation of PML-RAR protein, (2) transformation of PML-RAR from transcription repressor to activator, and (3) differentiation. Retinoic acid syndrome may occur with fever, respiratory distress, interstitial pulmonary infiltrates, pleural and pericardial effusion, episodic hypotension, acute renal failure, and weight gain. Arsenic trioxide can be used upfront (with ATRA) and for **recurrent disease** but is associated with QT prolongation and sudden death

Acute Lymphoblastic Leukemia

NEJM 2006 354:2

PATHOPHYSIOLOGY

HISTOLOGIC TYPE

- **FAB L1**—small, uniform lymphoblasts with indistinct nucleoli
- **FAB L2**—larger, pleomorphic lymphoblasts with low nucleus to cytoplasm ratio and clear nucleoli
- **FAB L3**—large, pleomorphic lymphoblasts with basophilic cytoplasm, large nucleoli, vacuoles

WHO CLASSIFICATION

- **PRECURSOR B CELL** (L1, L2)
- **PRO-B ALL**—resembles an early stage of B cell
- **PRE-B-CELL ALL**—intracytoplasmic immunoglobulin
- **B-CELL ALL**—express surface immunoglobulin
- **PRECURSOR T CELL** (L1, L2)
- **BURKITT-LIKE ALL** (L3)

RISK FACTORS FOR ALL—age, previous chemotherapy or radiation, Down's syndrome

CLINICAL FEATURES

PANCYTOPENIA—weakness, fatigue, infections, gingival bleed, ecchymosis, petechiae, epistaxis, menorrhagia

ORGAN INVOLVEMENT—lymphadenopathy, hepatomegaly, splenomegaly, bone pain, cranial nerve palsies, headaches

NOTE: precursor B lymphoblastic lymphoma is associated with lymphadenopathy/extranodal involvement and < 25% blasts, while precursor T LBL is associated mediastinal mass and < 25% blasts

DISTINGUISHING FEATURES BETWEEN AML AND ALL

	AML	Precursor ALL
Blasts	Larger	Small
Auer rods	+	–
TdT	–	+
Myeloperoxidase	+	–

INVESTIGATIONS

BASIC

- **LABS**—CBCD, smear, lytes, urea, Cr, Ca, PO_4, Mg, uric acid, albumin, urinalysis, LDH, INR, PTT, fibrinogen, flow cytometry of peripheral blood (immunophenotyping)
- **BONE MARROW BIOPSY**—> 20% blast, flow cytometry for immunophenotyping, cytogenetic analysis (detection of BCR–ABL fusion and chromosomal abnormalities with pulsed-field gel electrophoresis and/or RT-PCR)
- **LUMBAR PUNCTURE**—CSF for cytology
- **TISSUE BIOPSY**—lymph node, skin, mediastinal mass

SPECIAL

- **IMAGING**—MUGA scan to evaluate cardiac function prior to anthracycline therapy
- **HLA TESTING**—to assist in obtaining HLA-matched platelets if needed during treatment and to find HLA-matched allogeneic bone marrow

PROGNOSTIC ISSUES

PROGNOSTIC FACTORS—while childhood ALL is curable in 85% of cases, adult ALL has a worse prognosis, with a 5-year survival of 35%. Factors associated with poorer survival include the following:

- **CLINICAL**—lack of response to induction therapy (most important), old age, leukocyte count, CNS involvement
- **CYTOGENETICS**—BCR–ABL fusion or t(9;22) (also known as the Philadelphia chromosome, in 20–50% of adults), MLL–AF4 fusion or t(4;11) (in 5–6% of adults), t(8;14), t(1;19), hypodiploidy (<45 chromosomes/cell), del(7), trisomy
- **FAVORABLE PROGNOSIS**—hyperdiploidy, del(9), TELAML1 fusion or t(12;21) (in 10% of adults)

PROGNOSTIC ISSUES (CONT'D)

RISK CATEGORIES

- **HIGH RISK**—any of age >60, t(9;22) or *bcr–abl*, t(4;11), t(1;19); WBC $>30\times10^3/\mu L$ in B-ALL or $>100\times10^3/\mu L$ in T-ALL or pro-B ALL
- **STANDARD RISK**—none of high-risk features

RISK FACTORS FOR CNS RELAPSE—high-risk genetic features, T-ALL, large tumor burden, CSF positivity

MANAGEMENT

REMISSION INDUCTION THERAPY—combination chemotherapy with high-dose cyclophosphamide, prednisone, vincristine, ananthracycline ± asparaginase. Complete response 80–90%. Management of specific subgroups include

- **PH + ALL**—add imatinib
- **L3 B-CELL ALL**—treat like Burkitt's lymphoma
- **T-CELL ALL**—treat with cyclophosphamide-containing regimens

CNS PROPHYLAXIS—to start after remission with intrathecal methotrexate with high-dose systemic methotrexate. Consider cranial radiation for patients at high risk of CNS relapse

MANAGEMENT (CONT'D)

INTENSIFICATION/CONSOLIDATION THERAPY

- **STANDARD RISK**—consolidation chemotherapy with various combinations of cyclophosphamide, 6-mercaptopurine, cytarabine, vincristine, and doxorubicin
- **HIGH RISK**—SCT if donor available and eligible for transplant; otherwise, consolidation chemotherapy

MAINTENANCE THERAPY—POMP (6-mercaptopurine daily, methotrexate weekly, vincristine and prednisone monthly) or dexamethasone for 2–3 years, except for patients who received allogeneic SCT

TREATMENT ISSUES

SURVIVORSHIP ISSUES—risk of secondary malignancies, neurologic sequelae, cardiotoxicity, infertility, depression, anxiety, and fatigue

Related Topics
Febrile Neutropenia (p. 263)
Tumor Lysis Syndrome (p. 254)

Chronic Lymphocytic Leukemia NEJM 2005 352:8

DIFFERENTIAL DIAGNOSIS OF LYMPHOCYTOSIS

NEOPLASTIC

- **CHRONIC LYMPHOCYTIC LEUKEMIA** (CLL, most common cause)
- **PROLYMPHOCYTIC LEUKEMIA**
- **LEUKEMIC PHASE OF LYMPHOMAS**—mantle cell lymphoma, lymphoplasmacytic lymphoma, follicular lymphoma, marginal zone lymphoma, hairy cell leukemia
- **LARGE GRANULAR CELL LYMPHOCYTE LEUKEMIA**

INFECTIONS—pertussis, infectious mononucleosis, CMV, hepatitis, toxoplasmosis

PATHOPHYSIOLOGY

WHO CLASSIFICATION—CLL is identical to small lymphocytic lymphoma (SLL, mature B-cell non-Hodgkin's lymphoma). Traditionally, CLL diagnosis is made from peripheral blood, while SLL diagnosis is made from lymph node biopsy

TRANSFORMATION OF CLL—prolymphocytic leukemia 10%, diffuse large B-cell lymphoma (Richter's transformation) 3–10%, Hodgkin's disease 0.5%, multiple myeloma 0.1%

CLINICAL FEATURES

ORGAN INFILTRATION—lymphadenopathy (80%), splenomegaly (50%), hepatomegaly, skin and lung infiltration, gastric erosions

PERIPHERAL BLOOD—lymphocytosis with smudge cells, anemia, thrombocytopenia

CONSTITUTIONAL—weight loss, fever, night sweats, fatigue, anorexia

ASSOCIATED SYNDROMES—ITP, hemolytic anemia, pure red cell aplasia, cryoglobulinemia, MPGN, hypogammaglobulinemia, monoclonal gammopathy

SECOND MALIGNANCIES—non-melanoma skin cancer 4.7%, sarcomas 3.3%, kidney 2.8%, lung 2%, prostate 1.5%

INVESTIGATIONS

BASIC

- **LABS**—CBCD, smear (smudge cells), lytes, urea, Cr, Ca, PO_4, Mg, uric acid, LDH, β2 microglobulin, albumin, quantitative immunoglobulin, serum protein electrophoresis, urinary protein electrophoresis

INVESTIGATIONS (CONT'D)

- **PERIPHERAL BLOOD FLOW CYTOMETRY FOR SURFACE MARKERS**

SPECIAL

- **BONE MARROW BIOPSY**
- **LYMPH NODE BIOPSY**
- **MICROBIOLOGY**—monospot test, hepatitis serology if need to rule out other causes

DIAGNOSTIC AND PROGNOSTIC ISSUES

NCI WORKING GROUP DIAGNOSTIC CRITERIA

- **PERIPHERAL BLOOD**—absolute lymphocyte count in the $>5\times10^3/\mu L$, with ≥1 B-cell marker (CD19, CD20, CD23) and CD5; >55% atypical cells
- **BONE MARROW**—a normocellular to hypercellular marrow with >20% clonal lymphocytes. Interstitial/nodular pattern (70%) has a better prognosis than diffuse/extensive pattern (30%)
- **IMMUNOPHENOTYPE**—CD5+, CD19+, CD20+ dim, CD23+, CD43+, CD10–, SIg+dim
- **NOTE**—for patients with lymphocyte count $5–10\times10^3/\mu L$, lymphocyte phenotyping is required

RAI STAGING

0 lymphocytosis in blood or bone marrow. Median survival >150 months

I lymphocytosis + lymphadenopathy. Median survival 101 months

II lymphocytosis + organomegaly. Median survival 71 months

III lymphocytosis + anemia (<110 g/L [<11 g/dL]). Median survival 19 months

IV lymphocytosis + thrombocytopenia ($<100\times10^3$/mL). Median survival 19 months

BINET STAGING

A <3 lymphoid-bearing sites enlarged. Median survival >10 years

B ≥3 lymphoid-bearing sites enlarged. Median survival 5 years

C anemia (<100 g/L [10 g/dL]) or thrombocytopenia ($<100\times10^3/\mu L$). Median survival 2 years

ADVERSE PROGNOSTIC FACTORS OF CLL—higher Rai stage, high Binet stage, diffuse pattern on bone marrow biopsy, lymphocyte doubling time <1 year (5-year survival vs. 12-year survival), CD38+, unmutated IgV_H genes, ZAP70 positive, 17p deletion, 11q deletion, trisomy 12

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

FEATURES SUGGESTIVE OF TRANSFORMATION—*new onset* localized lymph node enlargement, B symptoms (without obvious increase in tumor burden), hypercalcemia, elevation in LDH, or extranodal disease other than bone marrow and liver, rapid increase of splenomegaly, rapid elevation of lymphocytosis

MANAGEMENT

AGE<65 AND OTHERWISE HEALTHY (potentially curative)—consider high-dose chemotherapy + allogeneic stem cell transplant

AGE>65 OR COMORBIDITIES (palliative)—first-line regimens include **FR** (fludarabine, rituximab) **or FCR** (fludarabine, cyclophosphamide, rituximab). Second line therapy includes mainly **alkylating agents** (chlorambucil, cyclophosphamide, CVP). **Alemtuzumab** (anti-CD52 antibody), **bendamustine** or **ibrutininb** (bruton's tyrosine kinase inhibitor) are useful for fludarabine-refractory disease. **Indications for treatment** include symptoms (weakness, painful lymphadenopathy, B symptoms, symptomatic splenomegaly), anemia (Hb <110 g/L [<11 g/dL]), thrombocytopenia (platelets $<100\times10^3/\mu L$), autoimmune hemolytic anemia/thrombocytopenia that failed steroids, progressive disease (increasing lymphocytosis with doubling time <6 months ± rapidly enlarging lymph nodes, spleen, and liver). If evidence of Richter's transformation, treat as aggressive lymphoma with R-CHOP

NOTE—while traditionally SLL has been managed as a low-grade non-Hodgkin's lymphoma, it is identical to CLL and should be treated as such

TREATMENT ISSUES

NCI WORKING GROUP DIAGNOSTIC CRITERIA FOR TREATMENT RESPONSE

- **COMPLETE RESPONSE**—normal physical examination and no symptoms. Lymphocytes $\leq4\times10^3/\mu L$, neutrophils $\geq1.5\times10^3/\mu L$, platelets $>100\times10^3/\mu L$, Hb >110 g/L [>11 g/dL], and bone marrow lymphocytes <30% with no nodules. Duration of at least 2 months
- **PARTIAL RESPONSE**—nodes/liver/spleen ≥50% decrease PLUS one of neutrophils $\geq1.5\times10^3/\mu L$, platelets $>100\times10^3/\mu L$, or Hb >110 g/L [>11 g/dL] or 50% improvement. Duration of at least 2 months
- **STABLE DISEASE**—between PR and PD
- **PROGRESSIVE DISEASE**—any one of nodes/liver/spleen ≥50% increase or new lesions, lymphocytes ≥50% increase, or Richter's syndrome

SPECIFIC ENTITIES

HAIRY CELL LEUKEMIA

- **PATHOPHYSIOLOGY**—rare indolent non-Hodgkin's lymphoma with mononuclear cells displaying cytoplasmic projections giving a hairy appearance. Secretes fibronectin, cytokines, and TNF-causing bone marrow fibrosis
- **CLINICAL FEATURES**—splenomegaly (90%), tricytopenia (fatigue, recurrent infections, thrombocytopenia), and lymphocytosis. Lymphadenopathy is uncommon
- **TREATMENTS**—treat only if symptomatic (cytopenia, splenomegaly, B symptoms). Cladribine (2Cda) is first-line treatment and may be repeated. Other treatments include pentostatin, interferon, splenectomy and rituximab

Hodgkin's Lymphoma

PATHOPHYSIOLOGY

HISTOLOGIC TYPE

- **CLASSICAL HODGKIN'S LYMPHOMA** (95%)—B-cell lymphoma characterized by the presence of Reed–Sternberg cells. CD15 and CD30 positive. Spreads in orderly fashion to contiguous nodal regions
  - **NODULAR SCLEROSIS** (70%)—more common in females, above diaphragm involvement (mediastinal mass). Three grades include lymphocyte predominant (G1), mixed (G2), and syncytial (G3)
  - **MIXED CELLULARITY** (20–25%)—more common in men. Tend to be EBV+. Retroperitoneal disease. Worse prognosis
  - **LYMPHOCYTE RICH** (5%)—more common in older males, peripheral lymph nodes. Excellent prognosis
  - **LYMPHOCYTE DEPLETED** (2%)—liver and marrow involvement with relative sparing of lymph nodes. Worse prognosis
- **NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN'S LYMPHOMA** (5%)—males, upper neck involvement. Characterized by popcorn cells. Slow progression, excellent prognosis. CD20 positive

RISK FACTORS

- **FAMILY HISTORY**
- **ENVIRONMENTAL**—wood workers, farmers, meat workers
- **DISEASES**—mononucleosis (EBV infection 3×), AIDS, bone marrow transplant

CLINICAL FEATURES

SYMPTOMS

- **MASS EFFECT**—lymphadenopathy, hepatosplenomegaly, mediastinal/abdominal/pelvic masses may cause local destruction, obstruction, and compression
- **HEMATOLOGIC**—anemia, thrombocytopenia, lymphocytosis, eosinophilia

CLINICAL FEATURES (CONT'D)

- **CONSTITUTIONAL**—B-symptoms specifically refer to weight loss >10% over 6 months, fever >38 °C [>100.4 °F], and drenching night sweats. Other constitutional symptoms include fatigue, anorexia, pruritus
- **PARANEOPLASTIC SYNDROMES**—**alcohol-induced pain**, **skin** (skin infiltration, erythema multiforme, erythema nodosum, necrotizing lesions, ichthyosis, acrokeratosis, urticaria), **neurologic** (paraneoplastic cerebellar degeneration, chorea, limbic encephalitis, subacute sensory neuropathy, subacute lower motor neuropathy, stiff man syndrome), **renal** (minimal change disease, FSGS), **hypercalcemia**

DISTINGUISHING FEATURES BETWEEN MALIGNANT AND NON-MALIGNANT LYMPHADENOPATHY

	Malignancy	Benign
Size	Larger, grows	Smaller (<1 cm)
Consistency	Rubbery, firm	Soft
Mobility	Immobile	Mobile
Matted	Yes	No
Tenderness	No	Yes

STAGING

COTSWOLDS STAGING (MODIFIED FROM ANN ARBOR STAGING)

I Single node region or lymphoid structure (spleen, thymus, Waldeyer's ring)

II Two or more node regions on the same side of diaphragm. All nodal disease within the mediastinum is considered to be a single lymph node region and hilar involvement constitutes an additional site of involvement.
The number of anatomic regions should be indicated by a subscript (e.g. II_2)

STAGING (CONT'D)

III Involvement on both sides of diaphragm. III_1 indicates involvement of the spleen or splenic hilar, celiac, or portal nodes. Stage III_2 indicates involvement of the paraaortic, iliac, inguinal, or mesenteric nodes

IV Diffuse or disseminated foci of involvement of one or more extralymphatic sites (e.g. bone marrow, extranodal sites that cannot be included in one radiation field)

DESIGNATIONS

E—extralymphatic site (i.e. involvement outside of lymph nodes, spleen, thymus, and Waldeyer's ring) or involvement by direct extension

X—bulky disease defined as mediastinal mass >1/3 of internal transverse diameter of the thorax at the level of T5/6 interspace or >10 cm [>3.9 in.] maximum dimension of a nodal mass

A—no B symptoms

B—weight loss >10% over 6 months, fever >38 °C [>100.4 °F], drenching night sweats

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, lytes, urea, Cr, AST, ALT, ALP, bilirubin, Ca, LDH, ESR, albumin, quantitative immunoglobulin, serum protein electrophoresis, HCV, HBV, and HIV serology
- **IMAGING**—CXR, CT chest/abdomen/pelvis, PET scan
- **LYMPH NODE BIOPSY**—referral to surgery

SPECIAL

- **BONE MARROW BIOPSY**—if B symptoms, Hb <120 g/L [<12 g/dL] in women, Hb <130 g/L [<13 g/dL] in men, WBC $<4\times10^3/\mu L$, platelets $<125\times10^3/\mu L$
- **ENT EXAMINATION**—stage IA or IIA with upper cervical lymph node involvement
- **MRI SPINE**—if suspect spinal cord compression
- **MUGA SCAN OR ECHOCARDIOGRAM**—evaluate cardiac function prior to anthracycline therapy
- **GALLIUM SCAN**—stage IA or IIA without intrathoracic involvement

PROGNOSTIC ISSUES

PROGNOSTIC FACTORS FOR EARLY STAGE DISEASE—age >50, bulky disease, ESR >50 mm/h without B symptoms or ESR >30 mm/h with B symptoms, anemia

INTERNATIONAL PROGNOSTIC FACTOR PROJECT SCORE FOR ADVANCED HODGKIN'S LYMPHOMA (HASENCLEVER SCORE)

- **FACTORS**—age >45, male gender, Ann Arbor clinical stage IV, albumin <40 g/L [<4 g/dL], hemoglobin <105 g/L [<10.5 g/dL], WBC $>15\times10^3/\mu L$, lymphocyte $<0.6\times10^3/\mu L$, or <8% of total WBC count
- **SCORING**—1 point per factor, with a score of 0–7
- **UTILITY**—the 5-year progression-free survival was 84, 77, 67, 60, 51, 42% for scores of 0, 1, 2, 3, 4, and 5–7, respectively

MANAGEMENT

LIMITED STAGE (stage IA, IIA, and IB in some institutions, 30%)—ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) *x*2 cycles. PET scan afterward, if complete remission, 2 more cycles; otherwise, give involved field radiation. If stage IA low bulk high neck (above hyoid) or epitrochlear nodular lymphocyte predominant disease, involved field radiation only

ADVANCED STAGE (70%)—ABVD×6 cycles. Reassess with CT and/or PET scan. If residual disease, consider involved field irradiation. Alternative regimens include BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) combined with involved field radiotherapy or Stanford V regimen (doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, prednisone) combined with involved field radiotherapy

REFRACTORY OR RELAPSED DISEASE—brentuximab (anti-CD30 antibody conjugated to auristatin), high-dose chemotherapy with CBV (cyclophosphamide, BCNU, etoposide) or BEAM (BCNU, etoposide, cytarabine, melphalan) and irradiation plus autologous stem cell transplant. Overall, 40–50% of refractory disease and 60–70% of first relapse can be cured

TREATMENT ISSUES

INDICATIONS FOR AUTOLOGOUS STEM CELL TRANSPLANT—progression during first- or second-line chemotherapy, relapse <1 year after

TREATMENT ISSUES (CONT'D)

completion of chemotherapy, relapse with B symptoms or extranodal sites. Patients with relapse >1 year or only in previously unirradiated lymph nodes may or may not require transplant

TREATMENT ISSUES (CONT'D)

FOLLOW-UP—every 3 months for the first 2 years, every 6 months for the next 3 years, then annually. Pay particular attention to relapse (10–30%), hypothyroidism (50%), dental caries, and second malignancies (breast, lung, esophageal, stomach, thyroid, melanoma, cervical, AML)

Non-Hodgkin's Lymphoma

DIFFERENTIAL DIAGNOSIS OF LYMPHADENOPATHY

INFECTIONS

- **BACTERIAL**—local infections, brucellosis, leptospirosis, lymphogranuloma venereum, typhoid fever
- **ATYPICAL**—TB, syphilis, Lyme disease
- **VIRAL**—HIV, EBV, HSV, CMV, HBV, mumps, measles, rubella, dengue fever
- **FUNGAL**—histoplasmosis, coccidioidomycosis, cryptococcosis
- **PARASITIC**—toxoplasmosis

NEOPLASTIC

- **LYMPHOMA**—Hodgkin's, non-Hodgkin's
- **LEUKEMIA**
- **METASTATIC CANCER**
- **LYMPHOPROLIFERATIVE**—Castleman's disease, angioimmunoblastic lymphadenopathy, autoimmune lymphoproliferative disease

INFLAMMATORY—RA, SLE, dermatomyositis, Still's disease, Churg–Strauss syndrome

INFILTRATIVE—sarcoidosis, amyloidosis, histiocytosis, chronic granulomatous disease

OTHERS—**medications** (phenytoin), **endocrine** (hypothyroidism, Addison's disease), serum sickness

PATHOPHYSIOLOGY

HISTOLOGIC TYPE (WHO CLASSIFICATION)

- **INDOLENT B-CELL LYMPHOMAS**
  - **FOLLICULAR LYMPHOMA** (FL, 25%)—grade I (0–5 centroblasts/high power field), II (6–15 centroblasts/high power field), IIIA (>15 centroblasts/high power field, centrocytes present)
  - **MARGINAL ZONE LYMPHOMA** (MZL, 5%)—MALT, nodal, splenic
  - **MANTLE CELL LYMPHOMA** (MCL, 7%)—mantle zone, nodular, diffuse, blastoid variant

PATHOPHYSIOLOGY (CONT'D)

  - **SMALL LYMPHOCYTIC LYMPHOMA** (SLL, 5–10%)—identical to chronic lymphocytic leukemia in pathologic characteristics, but treated as low grade B-cell lymphoma
  - **HAIRY CELL LEUKEMIA** (HCL)
  - **LYMPHOPLASMACYTIC LYMPHOMA** (LPL, 2–3%)—also called Waldenstrom's macroglobulinemia
  - **PLASMA CELL MYELOMA/PLASMACYTOMA** (MM)
- **AGGRESSIVE B-CELL LYMPHOMAS**
  - **FOLLICULAR LYMPHOMA** (FL)—grade IIIB (sheets of centroblasts)
  - **DIFFUSE LARGE B-CELL LYMPHOMA** (DLBCL, 30–40%)—clinical subtypes include primary mediastinal B-cell lymphoma, primary effusion lymphoma (HHV8), and intravascular B-cell lymphoma. Pathologic subtypes include T-cell -rich B cell lymphoma, anaplastic large cell lymphoma, centroblastic, and immunoblastic
  - **DOUBLE-HIT DLBCL** (both c-myc and bcl2 translocations)
- **LEUKEMIC B-CELL LYMPHOMAS**
  - **BURKITT'S LYMPHOMA** (BL)
  - **PRECURSOR B LYMPHOBLASTIC LYMPHOMA** (ALL)
- **INDOLENT T-CELL LYMPHOMAS**
  - **MYCOSIS FUNGOIDES** (MF)
  - **PRIMARY CUTANEOUS ANAPLASTIC LARGE CELL** (PCALC)
  - **LYMPHOPROLIFERATIVE DISEASE OF LARGE GRANULAR LYMPHOCYTES** (LGL)
- **INDOLENT NATURAL KILLER CELL LYMPHOMAS**
  - **NATURAL KILLER CELL LARGE GRANULAR LYMPHOCYTE LEUKEMIA** (NK-LGL)
- **AGGRESSIVE T-CELL LYMPHOMAS**
- **PERIPHERAL T-CELL LYMPHOMA, NOT OTHERWISE SPECIFIED** (PTCL-NOS)

PATHOPHYSIOLOGY (CONT'D)

- **PERIPHERAL T-CELL LYMPHOMA, SPECIFIED**—angioimmunoblastic (AILD++ type), nasal T/NK-cell type, subcutaneous panniculitic, intestinal enteropathy associated, hepatosplenic, anaplastic large cell including null cell
- **LEUKEMIC T-CELL LYMPHOMAS**
  - **ADULT T-CELL LYMPHOMA/LEUKEMIA** (HTLV)
  - **PRECURSOR T LYMPHOBLASTIC**
  - **LEUKEMIA/LYMPHOMA**

RISK FACTORS

- **FAMILY HISTORY**
- **ENVIRONMENTAL**—previous immunosuppressive therapy, radiation, allogeneic stem cell transplant, pesticides, agricultural chemicals, smoking, hair dyes, geography (e.g. risk of Burkitt's lymphoma is 50× higher in Africa than in the USA)
- **DISEASES**—infections (HIV, EBV, HHV8, HCV, HTLV, *Helicobacter pylori*), inflammatory disorders (RA, SLE, Sjogren's syndrome, mixed cryoglobulinemia, inflammatory bowel disease), inherited immune defects

CLASSIC TRANSLOCATIONS IN LYMPHOMA

- **MANTLE CELL LYMPHOMA**—t(11;14) in 95%, cyclin D1 (bcl1)
- **FOLLICULAR LYMPHOMA**—t(14;18) in 85%, anti-apoptotic protein (bcl2)
- **DIFFUSE LARGE CELL LYMPHOMA**—t(3;14) in 40%, zinc finger transcription factor (bcl6)
- **MALT**—t(1;14) in < 5%, bcl10
- **BURKITT'S LYMPHOMA**—t(8;14), t(2;8), or t(8;22) in 100%, c-myc overexpression

INFECTIONS AND LYMPHOMA

- **EBV**—Hodgkin's lymphoma, Burkitt lymphoma, post-transplant lymphoproliferative disorders, primary CNS lymphoma
- **HCV**—splenic marginal zone lymphoma
- **HHV8** (also known as Kaposi's Sarcoma Herpes Virus)—Castleman disease, primary effusion lymphoma
- **HIV**—primary CNS lymphoma
- **HTLV**—adult T-cell leukemia/lymphoma
- ***BORRELIA BURGDORFERI***—cutaneous marginal zone lymphoma
- ***CAMPYLOBACTER JEJUNI***—small bowel marginal zone lymphoma
- ***CHLAMYDIA PSITACCI***—eye marginal zone lymphoma
- **H. PYLORI**—gastric MALT

TRANSFORMATION OF INDOLENT LYMPHOMA—10% of SLL, MZL, and LPL and 60% of FL eventually transform into aggressive DLBCL. Features suggestive of transformation include rapid local progression, progression at unusual extranodal sites (CNS, lungs, soft tissue), acute rise in LDH, hypercalcemia, and new onset B symptoms

CLINICAL FEATURES

SYMPTOMS

- **MASS EFFECT**—lymphadenopathy (occipital, posterior auricular, preauricular, mandibular, submental, cervical, supra- and infraclavicular, Waldeyer's ring [tonsils, base of tongue, nasopharynx], epitrochlear, axillary, inguinal, popliteal), hepatosplenomegaly, mediastinal/abdominal/pelvic/testicular/CNS masses may cause local destruction, obstruction, and compression
- **HEMATOLOGIC**—anemia, thrombocytopenia, neutropenia, lymphocytosis
- **CONSTITUTIONAL**—B-symptoms. Other constitutional symptoms include fatigue, anorexia, pruritus
- **PARANEOPLASTIC SYNDROMES**

NOTE: lymphoma can mimic many diseases. Always have a high index of suspicion for lymphoma, particularly if B symptoms or multisystem involvement

STAGING

TUMOR BURDEN—a combination of stage, bulkiness (>10 cm in greatest diameter), B symptoms

ANN ARBOR STAGE

I Single node region

II Two or more node regions on same side of diaphragm

III Involvement on both sides of diaphragm

IV Diffuse or disseminated foci of involvement of one or more extralymphatic sites (e.g. bone marrow, extranodal sites that cannot be included in one radiation field)

DESIGNATIONS

E—single extralymphatic site (i.e. involvement outside of lymph nodes, spleen, thymus, and Waldeyer's ring) or involvement by direct extension

S—splenic involvement

A—no B symptoms

B—weight loss >10% over 6 months, fever >38 °C [100.4 °F], drenching night sweats

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, lytes, urea, Cr, AST, ALT, ALP, bilirubin, Ca, PO_4, Mg, uric acid, LDH, albumin, quantitative immunoglobulin, serum protein electrophoresis, HBV, HCV, and HIV serology
- **IMAGING**—CXR, CT chest/abdomen/pelvis, PET scan
- **LYMPH NODE BIOPSY**
- **BONE MARROW BIOPSY WITH FLOW CYTOMETRY FOR LYMPHOID SURFACE MARKERS**

SPECIAL

- **MRI SPINE**—if suspect spinal cord compression
- **MUGA SCAN OR ECHOCARDIOGRAM**—evaluate cardiac function prior to anthracycline therapy for patients with significant cardiac risk factors

DIAGNOSTIC AND PROGNOSTIC ISSUES

IMMUNOPHENOTYPE OF SELECTED LYMPHOMAS

	CLL	MCL	FL	MZL
CD20	+ dim	+	+	+
CD5	+	+	–	–
CD23	+	–	–	–
CD43	+	+	–	+
CD10	–	–	+	–

INTERNATIONAL PROGNOSTIC INDEX (IPI)

- **FACTORS**—age >60, serum LDH > normal, ECOG performance status ≥2, Ann Arbor clinical stage III or IV, extranodal disease sites ≥2 (defined as involvement of organs other than lymph nodes, spleen, thymus, and Waldeyer's ring)
- **SCORING**—1 point per factor, with a score of 0–5
- **UTILITY**—5-year overall survival approximately 73%, 51%, 43%, and 26% for IPI of 0–1, 2, 3, and 4–5. With the new revised IPI (post-rituximab era), 5-year overall survival 94%, 79%, and 55% for IPI of 0, 1–2, and 3–5, respectively

FOLLICULAR LYMPHOMA INTERNATIONAL PROGNOSTIC INDEX (FLIPI)

- **FACTORS**—age >60, serum LDH > normal, hemoglobin <120 g/L [<12 g/dL], Ann Arbor clinical stage III or IV, involved nodal sites >4
- **SCORING**—1 point per factor, with a score of 0–5

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

- **UTILITY**—for follicular lymphoma patients specifically; 5-year survival approximately 91%, 78%, and 52% for FLIPI of 0–1, 2 and 3–5, respectively

MANAGEMENT

INDOLENT LYMPHOMAS

- **LIMITED STAGE** (IA or IIA, 10%)—radiation (10-year survival 50%)
- **ADVANCED STAGE** (IB, IIB, III, IV, or any bulky disease, 90%)—if asymptomatic (40%), watchful waiting. If symptomatic or threatening disease (60%), R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) CVPR×8 cycles (cyclophosphamide, vincristine, prednisone, and rituximab), or R-bendamustine followed by maintenance rituximab for 2 years if PR. Other options include ibrutinib, fludarabine, cyclophosphamide, I^{131}-tositumomab, and Y^{90}-ibritumomab. Evaluation for SCT is appropriate

AGGRESSIVE LYMPHOMAS

- **LIMITED STAGE** (IA or IIA, 30%)—R-CHOP× 3 cycles. PET scan afterwards, if complete remission, one more cycle; otherwise, give involved field radiation
- **ADVANCED STAGE** (IB, IIB, III, IV, or any bulky disease, 70%)—R-CHOP×6. PET scan afterwards, if local residual disease, give involved field radiation; if diffuse residual disease, consider **salvage therapy** (see below). For patients with bone marrow/peripheral blood involvement, **intrathecal chemotherapy** may be considered as 5–20% chance of leptomeningeal disease otherwise
- **SALVAGE**—**GDPR** (gemcitabine, dexamethasone, cisplatin, rituximab) or **RICE** (rituximab, ifosfamide, carboplatin, etoposide), followed by **autologous stem cell transplant**

HIGHLY AGGRESSIVE LYMPHOMAS

- **BURKITT'S LYMPHOMA**—expedited staging (within 1–2 days). For **low-risk disease** (stage I or II, non-bulky <5 cm, no bone marrow/blood/CNS disease and normal LDH), give CODOX-MR (cyclophosphamide, doxorubicin, vincristine, methotrexate, rituximab)×1 then restage. If CR/PR, give IVAC-R (ifosfamide, etoposide, cytarabine)×1 then CODOX-MR×1; otherwise, give IVAC-R×1 then proceed to stem cell transplant. For **high-risk disease**, give CODOX-MR×1, IVAC-R×1 then restage. If CR/PR and no marrow infiltration at diagnosis, then autologous stem cell transplant;

MANAGEMENT (CONT'D)

otherwise, individualized higher intensity treatment. Allogeneic transplant may be considered (balance between time to find allogeneic donor and use of contaminated stem cells). A total of 8 doses of intrathecal chemotherapy should be given during treatment course. All patients should receive tumor lysis syndrome prophylaxis (hydration, allopurinol, rasburicase). Cure rate ~60%

- **ACUTE LYMPHOBLASTIC LYMPHOMA**—expedited staging (within 1–2 days). For most patients, allogeneic/autologous stem cell transplant plus intrathecal chemotherapy (allogeneic if leukemic, otherwise, autologous). Another option is the hyper-CVAD/methotrexate/cytarabine regimen. All patients should receive tumor lysis syndrome prophylaxis (hydration, allopurinol)

TREATMENT ISSUES

INTERNATIONAL WORKSHOP CRITERIA FOR TREATMENT RESPONSE FOR HODGKIN'S AND NON-HODGKIN'S LYMPHOMA

COMPLETE REMISSION (CR)—disappearance of all evidence of disease

- **Nodal masses:** if FDG-avid or PET positive prior to therapy, mass of any size permitted if PET negative. If variably FDG-avid or PET negative, regression to normal size on CT required
- **Liver and spleen:** not palpable, nodules disappeared
- **Bone marrow:** infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative

PARTIAL REMISSION (PR)—regression of measurable disease and no new sites

- **Nodal masses:** ≥50% decrease in sum of the product of the diameter (SPD) of up to 6 largest dominant masses; no increase in size of other nodes. If FDG-avid or PET positive prior to therapy, one or more PET positive at previously involved site; or if variably FDG-avid or PET negative, regression on CT ≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter)
- **Liver and spleen:** no increase in size
- **Bone marrow:** irrelevant if positive prior to therapy; cell type should be specified

STABLE DISEASE (SD)—failure to attain CR/PR or PD

- **Nodal masses:** if FDG-avid or PET positive prior to therapy, PET positive at prior sites of disease and no new sites on CT or PET. If variably FDG-avid or PET negative, no change in size of previous lesions on CT

RELAPSED DISEASE (RD) **OR PROGRESSIVE DISEASE** (PD)—any new lesion or increase by ≥50% of previously involved sites from nadir

- **Nodal masses:** appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node >1 cm in short axis. Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy
- **Liver and spleen:** >50% increase from nadir in the SPD of any previous lesions
- **Bone marrow:** new or recurrent involvement

JCO 2007 25:5

SPECIFIC ENTITIES

EYE LYMPHOMA

- **PATHOPHYSIOLOGY**—periorbital involvement (mostly MALT type) or intraocular involvement (usually DLBCL with more indolent course)
- **TREATMENTS**—for periorbital MALT, involved field radiation if localized disease or CVP if widespread disease. For intraocular disease, steroids, and involved field radiation. High-dose methotrexate may be useful

PRIMARY CNS LYMPHOMA

- **PATHOPHYSIOLOGY**—usually multifocal but confined to CNS. May have leptomeningeal or intraocular involvement. Frequently aggressive B-cell lymphoma
- **CLINICAL FEATURES**—focal neurological deficit, personality change, mild dementia, persistent headache
- **DIAGNOSIS**—CT or MRI head, lumbar puncture, slit lamp examination. If CNS lymphoma in the differential, try to avoid giving steroids before biopsy. Always check HIV
- **TREATMENTS**—high-dose corticosteroid with high-dose methotrexate is preferred. Whole brain radiation represents an alternative. Prognosis is 60% 2-year survival and 30% 5-year survival

LEPTOMENINGEAL MENINGITIS

- **RISK FACTORS**—aggressive lymphomas (lymphoblastic lymphoma, DLBCL, Burkitt's lymphoma, MCL), extranodal sites involvement (bone marrow, testicular, paranasal, retroperitoneal lymph nodes), any of the five IPI prognostic factors

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—jaw pain and numbness, radicular pain, back pain, neck pain/rigidity, confusion, cranial nerve deficits (especially II, III, V, VI, VII), focal weakness, sensory changes, headaches
- **DIAGNOSIS**—lumbar puncture with positive cytology (sens 60% with single attempt, 3 attempts for increased yield), gadolinium-enhanced MRI showing enhancement and enlargement of one or more cranial nerves due to tumor infiltration
- **TREATMENTS**—high-dose steroid (dexamethasone 12–20 mg PO/IV daily), radiation to the site of disease, intrathecal methotrexate, or cytarabine. Important to treat underlying systemic disease. Highly selected patients may benefit from high-dose chemotherapy with stem cell transplantation with better outcomes. Median survival after CNS recurrence is 3 months

LOCALIZED PARANASAL SINUS LYMPHOMA

- **PATHOPHYSIOLOGY**—usually DLBCL type. May involve CNS if invade through the base of skull
- **CLINICAL FEATURES**—local pain, rhinorrhea, nasal or upper airway obstruction, facial swelling, epistaxis, diplopia, visual loss
- **TREATMENTS**—R-CHOP × 3 + involved field radiation + intrathecal chemotherapy × 6

MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT)

- **PATHOPHYSIOLOGY**—extranodal marginal zone B-cell lymphomas that present with localized disease involving the GI tract, salivary glands, thyroid, orbit, conjunctiva, breast, and lung. Note that diffuse large cell lymphoma and mantle cell lymphoma also commonly involve GI mucosa
- **ASSOCIATIONS**—*H. pylori*-associated chronic gastritis, Celiac disease, Crohn's disease, gastrointestinal nodular lymphoid hyperplasia
- **DIAGNOSIS**—for gastric MALT, need to determine presence of *H. pylori* by biopsy (gastroscopy) ± urea breath test
- **TREATMENTS**—for *H. pylori*-positive gastric MALT, triple therapy may be adequate. Need to confirm eradication of *H. pylori*. Follow closely with gastroscopy. If MALT persists for over 8–12 months, should consider single-agent chemotherapy (cyclophosphamide, chlorambucil) or involved-field radiation. Partial gastrectomy may be needed for hemorrhage or perforation

ACUTE LYMPHOBLASTIC LYMPHOMA

- **PATHOPHYSIOLOGY**—continuum of presentation with acute lymphoblastic leukemia. Considered lymphoma if < 5% blasts in bone marrow; otherwise, considered leukemia
- **CLINICAL FEATURES**—usually mediastinal mass in young males

BURKITT'S LYMPHOMA

- **PATHOPHYSIOLOGY**—t(8;14, 2;8, 8;22) leading to c-myc overexpression
- **CLINICAL FEATURES**—usually advanced stage (80–90%). Abdominal mass, CNS, breast/ovarian involvement, and nodal sites but mediastinum usually spared

TESTICULAR LYMPHOMA

- **PATHOPHYSIOLOGY**—60% primary testicular lymphoma, 40% spread from other sites. Frequently DLBCL or immunoblastic subtype
- **CLINICAL FEATURES**—painless testicular mass in older man. High risk for recurrence, particularly CNS relapse
- **DIAGNOSIS**—scrotal US
- **TREATMENTS**—unilateral orchiectomy + R-CHOP + involved field radiation to scrotum + intrathecal chemotherapy if stage III/IV disease

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS (PTLD)

- **PATHOPHYSIOLOGY**—mostly of host origin and usually EBV positive (LMP-1 oncogene). EBV-negative PTLD present later and are more aggressive than EBV-positive PTLD. Mostly B-cell non-Hodgkin's lymphoma and very rarely T-cell or NK cell lymphomas
- **RISK FACTORS**—high degree of immunosuppression, pre-transplant EBV negativity. Risk highest in the first year, then reduces by 80%
- **CLINICAL FEATURES**—clinical spectrum includes reactive plasmacytic hyperplasia (55%, infectious mononucleosis like illness with no malignant transformation), polymorphic B-cell hyperplasia (30%, polyclonal cytogenetic abnormalities, immunoglobulin gene rearrangements, and disruption of underlying tissue architecture), and B- or T-cell lymphomas (15%, monoclonal malignancy)
- **TREATMENTS**—reduction in immunosuppression (may be sufficient for hyperplasia without monoclonal component), rituximab, chemotherapy (CHOP), antiviral agents, IVIG, surgical resection, radiation, interferon α, adoptive immunotherapy. Overall survival 25–35%. Prognostic factors include advanced age, performance status >1, involved site >1

MYCOSIS FUNGOIDES

- **PATHOPHYSIOLOGY**—indolent cutaneous T-cell lymphoma. Stages include premycotic, plaque,

SPECIFIC ENTITIES (CONT'D)

and tumor stage. Sezary syndrome is a systemic variant of mycosis fungoides with a triad of erythroderma, lymphadenopathy, and leukemia

- **CLINICAL FEATURES**—localized patches or plaques evolving into nodules and diffuse exfoliative erythroderma associated with abnormal circulating cells. Poor prognostic factors include extensive cutaneous disease (erythroderma), nodal spread, and extracutaneous involvement (liver, spleen, lung, GI tract)
- **TREATMENTS**—topical corticosteroids, topical nitrogen mustard, psoralen with UVA/UVB, bexarotene, radiation. Systemic treatments include CHOP, pentostatin, cladribine, fludarabine, IL-2, IFNα, alemtuzumab, liposomal doxorubicin

SYSTEMIC ANAPLASTIC LARGE CELL LYMPHOMA

- **PATHOPHYSIOLOGY**—may be T-cell, B-cell, or null cell type. Uniform expression of CD4, CD30, clusterin and epithelial membrane antigen (EMA). Anaplastic lymphoma kinase (ALK) overexpression associated with t(2;5) is a key prognostic marker (ALK+ 65–90% 5-year survival vs. ALK– 30–40% 5 year survival)
- **CLINICAL FEATURES**—ALK+ cases usually present at younger age with early disease. ALK– cases usually present at older age with advanced stage, elevated LDH, B symptoms, and extranodal sites
- **TREATMENTS**—CHOP-based regimens or brentuximab. Consider allogeneic stem cell transplant

CASTLEMAN'S DISEASE

- **PATHOPHYSIOLOGY**—lymphoid proliferation associated with POEMS syndrome, lymphomas (Hodgkin's, non-Hodgkin's), and Kaposi's sarcoma. HIV and HHV8 common in multicentric subtype
- **CLINICAL FEATURES**—unicentric (isolated lymphadenopathy, benign, HHV8 negative). Multicentric (fever, night sweats, fatigue, lymphadenopathy, pulmonary infiltrates, frequently HHV8 and HIV positive)
- **TREATMENTS**—unicentric (resection with high chance of cure, radiation, rituximab). Multicentric (rituximab, steroid, antivirals, anti-IL-6, CHOP)

Multiple Myeloma

NEJM 1997 336:23
NEJM 2004 351:18

TYPES OF PLASMA CELL DYSCRASIAS

MULTIPLE MYELOMA (75%)—malignant clone extends from pre-B-cell to plasma cell stage of differentiation. May produce IgG (60%), IgA (20%), or light chains (15%)

WALDENSTROM'S MACROGLOBULEMIA (20%)—proliferation of plasmacytoid lymphocytes (cell type that occurs earlier than plasma cell). Produces IgM. Now classified as lymphoplasmacytic lymphoma

HEAVY-CHAIN DEPOSITION DISEASE—IgA, IgG, or IgM heavy chain

LIGHT-CHAIN DEPOSITION DISEASE—κ or λ light chain

AL (PRIMARY) AMYLOIDOSIS—λ or κ light chain

PATHOPHYSIOLOGY

EPIDEMIOLOGY

- **INCIDENCE**—1%
- **MORTALITY**—1%

PATHOPHYSIOLOGY (CONT'D)

RISK FACTORS

- **PERSONAL**—old age, black race
- **DISEASES**—chronic polyclonal hypergammaglobulinemia
- **TREATMENT**—radiation

CLINICAL FEATURES

SYMPTOMS

- **PANCYTOPENIA**—weakness, fatigue, infections, gingival bleed, ecchymosis, epistaxis, menorrhagia
- **INCREASED POLYCLONAL PROTEIN**—infections due to ↓ normal Ig, hyperviscosity syndrome
- **LYTIC BONE LESIONS**—pain, fractures
- **HYPERCALCEMIA**—weakness, nausea, abdominal pain, polyuria, altered mental status
- **NEUROLOGIC**—peripheral neuropathy from amyloidosis, plasma cell infiltration of the meninges, cord compression, or radiculopathy from vertebral osteolytic lesions ± plasmacytoma

CLINICAL FEATURES (CONT'D)

- **RENAL FAILURE**
  - **PRE-RENAL**—N&V, renal vein thrombosis
  - **RENAL**—myeloma kidney (tubulointerstitial damage from increased light chain absorption at proximal tubule), plasma cell infiltration, Bence Jones/cast nephropathy, amyloidosis (λ), light-chain deposition disease (κ), hypercalcemia (nephrogenic DI), cryoglobulinemia, pyelonephritis, sepsis
  - **POST-RENAL**—renal stones (uric acid), neurogenic bladder
- **CONSTITUTIONAL**—anorexia, fatigue, weight loss

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, lytes, urea, Cr, Ca, β2 microglobulin, serum viscosity, quantitative immunoglobulin, albumin, serum protein electrophoresis (reciprocal depression), urinary protein electrophoresis, 24 h urinary collection for Bence Jones protein
- **IMAGING**—skeletal survey (NB: standard bone scan does NOT play a role in routine myeloma staging)
- **BONE MARROW BIOPSY**
- **NOTE**: light chain myeloma (20%) may have normal serum protein electrophoresis. Urinary Bence Jones protein (urine protein electrophoresis) is required to detect paraproteinemia; nonsecretory myeloma (3%) requires bone marrow biopsy for diagnosis

Related Topics
Amyloidosis (p. 483)
Renal Failure (p. 78)

DIAGNOSTIC AND PROGNOSTIC ISSUES

INTERNATIONAL MYELOMA WORKING GROUP CRITERIA

- **MULTIPLE MYELOMA**
  - **BONE MARROW PLASMA CELLS/PLASMACYTOMA**—no percent specified, but usually >10%
  - **M-PROTEIN**—in serum and/or urine, no concentration specified, but >30 g/L [>3 g/dL] in serum if overt myeloma
  - **TISSUE IMPAIRMENT**—★**CRAB**★ increased **c**alcium (>2.75 mmol/L [>11 mg/dL]), **r**enal insufficiency (Cr >173 μmol/L [>1.9 mg/dL]), **a**nemia (Hb <100 g/L [<10 g/dL] or drop by 20 g/L [2 g/dL]), **b**one lesions (lytic lesions, fractures). Other features include hyperviscosity, amyloidosis, or recurrent infections (>2 episodes in 12 months)
- **SMOLDERING MULTIPLE MYELOMA** (SMM)
  - **BONE MARROW PLASMA CELLS**— > 10%
  - **M-PROTEIN**— > 30 g/L [>3 g/dL] (but not necessary if bone marrow plasma cells > 10%)
  - **TISSUE IMPAIRMENT**—no symptoms
- **MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE** (MGUS)
  - **BONE MARROW PLASMA CELLS**—<10% (bone marrow biopsy is not required for suspected MGUS if M-protein ≤15 g/L [≤1.5 g/dL], IgG subtype, and patient asymptomatic)
  - **M-PROTEIN**— < 30 g/L [<3 g/dL]
  - **TISSUE IMPAIRMENT**—no symptoms
  - **COURSE**—occurs in 2% of population over age 50 and 3% over age 70. Rate of transformation to malignant plasma cell disorder (multiple myeloma, Waldenstrom's macroglobulinemia, primary amyloidosis, B-cell lymphoma, or chronic lymphocytic leukemia) is about 1% per year

NEJM 2006 355:26

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

DIAGNOSTIC CLUES

- **SYMPTOMS**—the presence of tissue impairment suggests either multiple myeloma (usually high M-protein) or amyloidosis (usually low M-protein). AL amyloidosis is characterized by insoluble, toxic amyloid precursor (light chains) aggregates that deposit in tissues in antiparallel β-pleated sheet configuration. The absence of symptoms suggests MGUS or SMM
- **QUANTITATIVE IG**—typically decreased serum levels of normal polyclonal immunoglobulins in multiple myeloma. However, this may also occur in MGUS
- **BENCE JONES PROTEINURIA**—the presence of monoclonal light chains (especially >1 g/day) in the urine suggests multiple myeloma. However, small amounts (<50 mg/day) may also occur in MGUS
- **SERUM M PROTEIN LEVEL**—the higher the level, the higher the likelihood of multiple myeloma. Some define 35 g/L [3.5 g/dL] for IgG and 20 g/L [2 g/dL] for IgA as cutoff, others define 30 g/L [3 g/dL] regardless of Ig subtype as cutoff

DURIE–SALMON STAGING FOR MULTIPLE MYELOMA

- **STAGE I** (low tumor burden, $<0.6 \times 10^{12}/m^2$)—all of Hb >100 g/L [>10 g/dL], $Ca^{2+} \leq 2.6$ mmol/L

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

[≤10.4 mg/dL], bones normal or solitary bone plasmacytoma only, IgG <50 g/L [<5 g/dL], IgA <30 g/L [<3 g/dL], and urinary λ or κ chains <4 g/day. Median survival ~60 months

- **STAGE II** (intermediate burden, $0.6–1.2 \times 10^{12}/m^2$)—between stages I and III. Median survival ~30 months
- **STAGE III** (high tumor burden, $>1.2 \times 10^{12}/m^2$)—any of Hb <85 g/L [<8.5 g/dL], Ca^{2+} >2.6 mmol/L [>10.4 mg/dL], >3 lytic lesions, plus one of IgG >70 g/L [>7 g/dL], IgA >50 g/L [>5 g/dL], or urinary λ or κ chains >12 g/day. Median survival ~15 months
- **SUBSTAGES**—A (Cr <175 μmol/L [<1.9 mg/dL]) and B (renal failure with Cr >175 μmol/L [>1.9 mg/dL])

PROGNOSTIC FACTORS FOR MULTIPLE MYELOMA—β2 microglobulin, albumin, platelet, creatinine, and age. The international staging system for multiple myeloma is particularly useful

- **STAGE I**—β2 microglobulin < 3.5 mg/L, albumin ≥35 g/L [≥3.5 g/dL]. Median survival 62 months
- **STAGE II**—neither stage I nor III. Median survival 44 months
- **STAGE III**—β2 microglobulin ≥5.5 mg/L. Median survival 29 months

JCO 2005 23:15

MANAGEMENT

MULTIPLE MYELOMA

- **AGE <65 AND OTHERWISE HEALTHY** (curative)—**induction chemotherapy** with bortezomib plus dexamethasone (first choice), lenalidomide plus dexamethasone, or bortezomib plus thalidomide plus dexamethasone, or bortezomib plus doxorubicin plus dexamethasone, or bortezomib plus lenalidomide plus dexamethasone. If good response, then proceed to **high-dose melphalan followed by autologous stem cell transplant**. Post-SCT maintenance therapy with lenalidomide is recommended
- **AGE >65 OR COMORBIDITIES** (palliative)—melphalan plus prednisone plus thalidomide, melphalan plus prednisone plus lenalidomide, or melphalan plus prednisone plus bortezomib, lenalidomide plus low dose dexamethasone or bortezomib plus dexamethasone. Addition of interferon to MP provides small benefit. If bony disease, add **bisphosphonate** (alendronate, zoledronate)

MANAGEMENT (CONT'D)

- **SUPPORTIVE MEASURES**—**hydration** (>3 L/day), **hypercalcemia** (hydration, *prednisone* 25 mg PO QID, pamidronate), **renal insufficiency** (treat underlying cause), **infections** (antibiotics, consider IVIG as last resort if recurrent infections despite prophylactic antibiotics), **skeletal lesions** (*pamidronate* 90 mg IV over 2 h q3–4weeks, radiation, vertebroplasty), **anemia** Hb <90 g/L [<9 g/dL] (transfusions, usually respond to an erythropoiesis stimulating agent, although one should exercise caution given the increased risk of thromboembolism and death), **hyperviscosity syndrome** (Ostwald viscosimeter >5, plasmapheresis), **prophylactic anticoagulation** (if on thalidomide/lenalidomide and chemotherapy)

SMM—no treatment. Follow clinically

MGUS—no treatment. Follow clinically

TREATMENT ISSUES

INDICATIONS FOR TREATING MULTIPLE MYELOMA—>stage I, increasing level of M-protein in serum or urine, significant hypercalcemia, anemia, renal insufficiency, lytic bone lesions, extramedullary plasmacytoma

SPECIFIC ENTITIES

SOLITARY PLASMACYTOMA OF BONE—single osteolytic bone lesion with limited amount of monoclonal protein in the serum or urine and absence of tissue impairment. Radiation is usually treatment of choice and may result in a cure. 80% chance of developing multiple myeloma

AMYLOIDOSIS—See p. 483 for more details. Workup include abdominal fat biopsy, abd US, and echocardiogram

POEMS SYNDROME—osteosclerotic myeloma with **P**olyneuropathy, **O**rganomegaly, **E**ndocrine (diabetes, hypothyroidism, parathyroid hypogonadism, HPA), **M**onoclonal protein, **S**kin changes (hyperpigmentation, hypertrichosis, acrocyanosis, plethora, hemangioma/telangiectasia). Polyneuropathy and monoclonal plasma cell disorder most important

HYPERVISCOSITY SYNDROME—IgG >70 g/L [>7 g/dL] or IgA >50 g/L [>5 g/dL]. Symptoms include fatigue, changes in mental status, focal or non-focal neurologic changes, visual changes along with retinopathy, angina pectoris, bleeding disorder, cryoglobulin, Raynaud's phenomenon, or purpuric eruptions on exposure to the cold

Febrile Neutropenia

See FEBRILE NEUTROPENIA (p. 263)

Hematopoietic Stem Cell Transplant

CMAJ 2004 170:10
NEJM 2006 354:17

TERMINOLOGIES

ALLOGENEIC TRANSPLANTATION (40%)—stem cells from HLA-matched sibling donor (25%) or unrelated donor (75%). The main advantage is graft vs. leukemia effect (GVL), while the main disadvantage is graft vs. host effect (GVHD)

AUTOLOGOUS TRANSPLANTATION (60%)—stem cells from self. The main advantage is lesser toxicity compared to allogeneic transplant, while the main disadvantage is possible contamination of the graft with malignant cells

HAPLOIDENTICAL TRANSPLANTATION (increasing use in adults)—stem cells from parent, child or sibling. Main advantage is the relative ease of identifying a donor, while the main disadvantage is graft rejection and GVHD

DONOR SOURCE—**peripheral blood** (10–20 L of blood, mobilization with GCSF, venipuncture, leukapheresis (up to 3 times for autologous stem cell transplant), faster engraftment, and improved overall survival (for autologous stem cell transplant and matched sibling allogeneic transplant), **bone marrow**, **umbilical cord blood** (expands supply of donors, although limited amount of stem cells in cord blood can affect engraftments and directs frequent use of "dual cord" transplantation; less GVHD with mismatches)

COMMON INDICATIONS

DECIDING BETWEEN ALLOGENEIC AND AUTOLOGOUS STEM CELL SOURCE—dependent on age, underlying disease, donor availability, institutional preference. In general, allogeneic transplant is more suitable for younger, healthier adults as it is more toxic but potentially more effective than autologous transplant

ALLOGENEIC—acute leukemia (50–70% cure if first remission, 10–30% cure if relapse), myelodysplastic syndrome (40–50% cure rate), chronic myeloid leukemia (50–70% cure if chronic phase, 10–30% cure if blast phase), chronic lymphocytic leukemia, indolent lymphoma, severe immunodeficiency syndromes, hemoglobinopathies

COMMON INDICATIONS (CONT'D)

AUTOLOGOUS—progressive Hodgkin's lymphoma (60–70% cure if relapse, 40–50% cure if refractory disease), multiple myeloma, relapsed and progressive large cell lymphoma, relapsed germ cell cancer

ALLOGENEIC TRANSPLANTATION

HUMAN LEUKOCYTE ANTIGEN MOLECULES—responsible for displaying endogenous and exogenous peptides to T cells. Mismatch between host and donor HLA type could result in graft vs. host disease, graft failure, or death. Note that transplant is not affected by differences in ABO blood groups

- **HLA CLASS I**—HLA-A, HLA-B, HLA-C
- **HLA CLASS II**—HLA-DR, HLA-DQ, HLA-DP

MATCHING PROCESS—ensure good match of HLA-A, HLA-B, HLA-C, DRB1, and DQB1. The chance of finding a sibling match is $1–0.75^n$, where n = number of siblings. The chance of finding a matched unrelated donor is >60%, higher for Caucasians and lower for other races. Search for a match typically takes 3–4 months

CONDITIONING—goal is to eradicate malignancy and suppress recipient's immune system to minimize rejection of donor's stem cells. Myeloablative regimens include cyclophosphamide plus total body irradiation (TBI) or high-dose busulfan. Reduced intensity regimens include fludarabine plus busulfan. Reduced intensity (also known as non-myeloablative or "mini" transplant) regimens use a milder conditioning regimen more tolerable for older patients (e.g. fludarabine plus cyclophosphamide, melphalan). Monitor toxicities closely during this time

- **HEMATOLOGIC**—pancytopenia, febrile neutropenia
- **EARLY NON-HEMATOLOGIC**—alopecia, N&V, oropharyngeal mucositis, diarrhea, sinusoidal obstruction syndrome (previously known as hepatic venoocclusive disease with tender hepatomegaly, jaundice and ascites), seizures, parotitis, pericarditis, cardiomyopathy, interstitial pneumonitis, hemorrhagic cystitis, rash

ALLOGENEIC TRANSPLANTATION (CONT'D)

- **LATE NON-HEMATOLOGIC**—hypothyroidism, sterility or premature menopause, growth impairment, dry eyes or mouth, cataracts, osteopenia or osteoporosis
- **FERTILITY**—infertility is almost certain in both men and women after TBI regimens, but not definite with non-TBI regimens. Consider oocyte/sperm/embryo cryopresevation
- **SECOND MALIGNANCIES**—increased incidence of solid tumors (bone, oropharynx, connective tissue, CNS, thyroid, melanoma), myelodysplastic syndrome, acute myelogenous leukemia, and lymphoproliferative disorders. Highest risks in patients with TBI

TRANSPLANTATION—infusion of stem cells over 30 min to 2 h

ENGRAFTMENT—typically happens between days +10 and +20. Defined as ANC $>0.5 \times 10^3/\mu L$, with platelet and RBC engraftment following. GCSF may be used in non-leukemic patients to accelerate engraftment by up to 1 week. Patient is supported with blood products and antimicrobial prophylaxis (e.g. ciprofloxacin for Gram negatives, trimethoprim–sulfamethoxazole for PJP, acyclovir for HSV, fluconazole for fungal agents) until engraftment occurs. Failure to engraft (primary graft failure) and irreversible decline of blood counts (secondary graft failure) are serious complications (<5%). For non-myeloablative transplant, perform chimerism analysis and consider either donor leukocyte infusion (DLI) or reducing immunosuppression to improve disease control

IMMUNE RECONSTITUTION—restoration of T-cell and B-cell immunity takes up to 12 months. Immunosuppressive treatment can usually be stopped within 1–3 years post-allogeneic transplant. Graft vs. host disease (GVHD) is a donor T-cell-mediated process. Overall transplant-related mortality is approximately 20–25%

GRAFT VS HOST DISEASE

- **ACUTE GVHD** (<100 days)—occurs in 40% of matched sibling and 80% of unrelated donor transplant. Symptoms include rash, hepatic dysfunction, diarrhea, vomiting. Mortality up to 80% in grade III and IV acute GVHD. Prophylaxis consisting of methotrexate and cyclosporine is usually used for anyone other than identical twins. Treatments include corticosteroids, cyclosporine, mycophenolate mofetil, tacrolimus, and antithymocyte globulin
- **CHRONIC GVHD** (>100 days)—an autoimmune syndrome occurs in up to 50% of matched sibling and >50% of unrelated donor transplant. Symptoms include oral and ocular changes (sicca), alopecia, cholestatic hepatic dysfunction, polyserositis, cutaneous scleroderma, and bronchiolitis obliterans. Treatments include corticosteroids and cyclosporine or tacrolimus for at least 6 months

INFECTIONS

- **PRE-GRAFTMENT** (<30 days)—HSV, Gram-negative bacteria, Gram-positive *Streptococcus*, fungal, central line infections (*S. epidermis*)
- **EARLY INFECTIONS** (30–100 days)—CMV, some fungal, PJP, central line infections (*S. epidermis*)
- **LATE INFECTIONS** (>100 days)—VZV, encapsulated bacteria, PJP, Aspergillus

AUTOLOGOUS TRANSPLANTATION

MATCHING PROCESS—not applicable

CONDITIONING—similar to allogeneic transplant. Regimens include CBV (cyclophosphamide, BCNU, etoposide), cyclophosphamide plus total body irradiation, and BEAM (BCNU, etoposide, cytosine arabinoside, melphalan)

TRANSPLANTATION—similar to allogeneic transplant, except stem cells obtained from patient pretransplant and cryopreserved

ENGRAFTMENT—similar to allogeneic transplant

IMMUNORECONSTITUTION—more rapid immune recovery and no GVHD. Overall transplant-related mortality is approximately 2%

LATE EFFECTS—MDS and AML in at least 10% of patients 5–10 years after autologous transplant

Related Topics
Acute Leukemia (p. 185)
Chemotherapy-Induced Diarrhea (p. 257)
Non-Hodgkin's Lymphoma (p. 193)
Febrile Neutropenia (p. 263)
Fungal Infections (p. 298)
Multiple Myeloma (p. 198)
Oral Mucositis (p. 256)
Sepsis (p. 111)
Tumor Lysis Syndrome (p. 254)

7
ONCOLOGY

Ahmed Eid, David Ramirez and Caren L. Hughes

Lung Cancer — NEJM 2004 350:4; NCCN Guideline 2014 version 4

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY

- **SMALL CELL** (SCLC, 15%)—mainly seen in smokers, central lesions, early metastasis compared to NSCLC
- **NON-SMALL CELL** (NSCLC, 85%)
  - **ADENOCARCINOMA** (50–60%)—women, may develop in nonsmokers, peripheral lesions. Bronchoalveolar (BAC) subtype may originate distal to grossly recognizable bronchi. BAC tends to be well differentiated, grows along intact alveolar septa, and has a propensity for aerogenous and lymphatic spread. May present as diffuse infiltration on chest X-ray
  - **SQUAMOUS** (25%)—mainly seen in smokers, central, cavitary lesions
  - **LARGE CELL** (15%)—peripheral lesions with prominent necrosis, slightly worse prognosis than squamous and adenocarcinoma
- **CARCINOID** (2%)—neuroendocrine origin. May cause airway obstruction, ectopic Cushing's, and carcinoid syndrome
- **CYSTIC ADENOID CARCINOMA**—locally invasive but may also metastasize
- **CARCINOSARCOMA**—localized lesion usually

RISK FACTORS

- **SMOKING**—30× increased risk compared to nonsmokers. Smokers have 30% lifetime risk of developing lung cancer. 85–90% of all lung cancers are related to smoking. Polymorphisms in carcinogen activating enzymes (*N-acetyltransferase* (NAT1 and NAT2), CYP 1A1 and 2A6) and inactivating enzymes (glutathione *S*-transferase S1 and M1) may contribute to individual susceptibility. The duration of smoking is a stronger risk factor than the number of cigarettes smoked. Cigar/pipe smoking (2×) and second-hand smoke (1.3×) are also risk factors
- **ENVIRONMENTAL**—asbestos (7×), arsenic, silica, chromium, nickel, polycyclic hydrocarbons, radon (10×), β-carotene supplements (in heavy smokers, 2–3×)
- **DISEASES**—tuberculosis, COPD, pulmonary fibrosis, previous radiation
- **FAMILY HISTORY**

CLINICAL FEATURES

LOCOREGIONAL—cough, sputum (salty suggests bronchoalveolar), hemoptysis, dyspnea, chest pain, wheezing, dysphagia, brachial plexus (Pancoast tumour), hoarseness, Horner's syndrome, superior vena cava syndrome

METASTATIC—bone pain, jaundice, seizures, headaches, adrenal lesions, skin lesions

CONSTITUTIONAL—weight loss, anorexia, fatigue

PARANEOPLASTIC SYNDROMES

	SCLC	Squamous	Adenocarcinoma	Large cell
SIADH	✓			
Ectopic Cushing's	✓			
Neurological syndromes[a]	✓			
Hypercalcemia		✓	✓	
Clubbing or hypertrophic osteoarthropathy		✓	✓	
Hypercoagulable state	✓	✓	✓	✓
Gynecomastia				✓

[a]Neurological syndromes associated with SCLC include dementia, cerebellar degeneration, limbic encephalopathy, optic neuritis and retinopathy, paraneoplastic sensory neuropathy (anti-Hu antibodies), and Eaton–Lambert syndrome

D. Hui et al. (eds.), *Approach to Internal Medicine: A Resource Book for Clinical Practice*,
DOI 10.1007/978-3-319-11821-5_7, © Springer International Publishing Switzerland 2016

STAGING

TNM STAGING (7TH EDITION)

T stage

- **T1** ≤3 cm without bronchoscopic evidence of invasion more proximal than the lobar bronchus
  - **T1a** ≤2 cm
  - **T1b** >2–3 cm
- **T2** >3 and ≤7 cm, or with any of the following: involving main bronchus ≥2 cm distal to the carina; invades visceral pleura; associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
  - **T2a** >3– ≤5 cm, or ≤5 cm but with any of the risk factors above
  - **T2b** >5–7 cm with or without any of the risk factors above
- **T3** >7 cm or invades chest wall, diaphragm, mediastinal pleura, parietal pericardium or main bronchus <2 cm to carina; atelectasis/obstructive pneumonitis of entire lung; separate tumor nodule(s) within the same lobe
- **T4** = invasion of mediastinum, heart, great vessels, carina, trachea, esophagus, or vertebral body; ipsilateral tumor nodule(s) in different lobes

N stage

- **N1** = ipsilateral peribronchial and/or hilar LN
- **N2** = ipsilateral mediastinal and/or subcarinal LN
- **N3** = ipsilateral supraclavicular and/or scalene or any contralateral LN

M stage (typically involves pleural fluid, lungs, brain, liver, adrenals, bones, and skin)

- **M1a** = malignant pleural effusion, pericardial effusion, separate tumor nodule(s) in contralateral lobe
- **M1b** = distant metastasis

STAGE GROUPINGS FOR LUNG CANCER

Stage	TNM @ = any	Median survival (months)	5-year survival
IA	T1aN0M0, T1bN0M0	60	50%
IB	T2aN0M0	43	43%
IIA	T1N1M0, T2aN1M0, T2bN0M0	34	36%
IIB	T2bN1M0, T3N0M0	18	25%
IIIA	T3N1M0, T1-3N2M0, T4N0-1M0	14	19%
IIIB	T@N3M0, T4N2M0	10	7%
IV	T@N@M1	6	2%

STAGING (CONT'D)

STAGING FOR SMALL CELL LUNG CANCER

- **LIMITED STAGE** (40%)—tumor confined to the hemithorax, mediastinum, and supraclavicular nodes, which can be encompassed within a tolerable radiation therapy port
- **EXTENSIVE STAGE** (60%)—non-limited stage, including pleural effusion

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, LDH, INR, PTT, Ca, albumin, CEA
- **IMAGING**—CXR (compared to old) and CT chest and upper abdomen (adrenals)
- **BIOPSY**—bronchoscopy with lavage/wash/brushings/biopsy (if central lesion), endobronchial US (EBUS) with biopsy (if suspect nodal disease), thoracentesis (if pleural effusion), CT-guided transthoracic needle aspiration (if peripheral lesion), mediastinoscopy (if any nodes on CT and potentially resectable disease, sens 90%, spc 100%), thoracotomy

SPECIAL

- **PET/CT**—sens 88%, spc 85%. Usually used for staging in patients with potentially resectable disease
- **PULMONARY FUNCTION TEST**—if surgical candidate
- **BONE SCAN**—if bone pain, elevated ALP or Ca, ≥N2
- **CT HEAD OR MR HEAD**—if ≥ N2 or symptomatic NSCLC, all SCLC
- **REPEATED SPUTUM CYTOLOGY**—sens 60–80% for central lesions, 15–30% for peripheral lesions

DIAGNOSTIC AND PROGNOSTIC ISSUES

REGIONAL LYMPH NODE CLASSIFICATION—based on mediastinoscopy. Nodes are designated 1–14. N3 node (supraclavicular) = position 1, N2 nodes = position 2–9, and N1 nodes = position 10–14

KARNOFSKY PERFORMANCE STATUS

PS	Function
100%	Normal, no complaints, no evidence of disease
90%	Able to carry on normal activity: minor symptoms of disease
80%	Normal activity with effort: some symptoms of disease
70%	Cares for self: unable to carry on normal activity or active work

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

PS	Function
60%	Requires occasional assistance but is able to care for needs
50%	Requires considerable assistance and frequent medical care
40%	Disabled: requires special care and assistance
30%	Severely disabled: hospitalization is indicated, death not imminent
20%	Very sick, hospitalization necessary: active treatment necessary
10%	Moribund, fatal processes progressing rapidly
0%	Dead

EASTERN CO-OPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

- **0**—normal. KPS 100%
- **1**—restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work. KPS 80–90%
- **2**—ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. KPS 60–70%
- **3**—capable of only limited self-care, confined to bed or chair >50% of waking hours. KPS 40–50%
- **4**—completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair. KPS 10–30%
- **5**—dead. KPS 0%

ADVERSE PROGNOSTIC FACTORS

- **GENERAL**—poor performance status (ECOG >1), involuntary weight loss (>5%), advanced stage, SCLC
- **POOR OUTCOME AFTER SURGERY**—poor performance status, weight loss (>5%), low FEV1, low P_aO_2, recent history of smoking

PROGNOSIS OF SMALL CELL LUNG CANCER—limited stage 20–40% 2-year survival, 16–24 months median survival, extensive stage <5% 2-year survival, 6–12 months median survival. Median survival post-relapse 4 months

MANAGEMENT

NON-SMALL CELL LUNG CANCER

- **STAGE IA**—**lobectomy**/**pneumonectomy**. Consider **stereotactic radiation** if inoperable
- **STAGE IB**—**lobectomy**/**pneumonectomy**. Consider adjuvant **chemotherapy** (e.g. cisplatin–vinorelbine × 4) if high-risk features (e.g. >4 cm, high grade, visceral pleural involvement, vascular invasion). Consider **stereotactic radiation** or **chemoradiation** if inoperable
- **STAGE II**—**lobectomy**/**pneumonectomy** + adjuvant **chemotherapy** [e.g. cisplatin–vinorelbine × 4, cisplatin-pemetrexed × 4 (if non-squamous)]
- **STAGE IIIA** (N2 disease)—**concurrent chemoradiation** [e.g. cisplatin–etoposide × 4, carboplatin-pemetrexed × 4 (if non-squamous)], followed by either **pneumonectomy**/**lobectomy** or **radiation boost**
- **STAGE IIIA** (unresectable) **AND IIIB**—no surgery. **Concurrent chemoradiation** [e.g. cisplatin–etoposide × 4, carboplatin-pemetrexed × 4 (if non-squamous)] with potential chance of cure. May consider sequential chemo-radiation but may have reduced chance of cure
- **STAGE IV**
  - **Palliative radiation**—should be administered before chemotherapy if patients present with symptomatic brain metastases, hemoptysis, SVC syndrome, severe bone pain or obstructive pneumonia
  - **First line systemic therapies**—for non-squamous histologies, consider erlotinib, gefitinib or afatinib (if EGFR+), crizotinib (if ALK+), or chemotherapy (e.g. cisplatin–pemetrexed × 4) followed by maintenance pemetrexed, bevacizumab or cetuximab. For squamous cell carcinoma, consider doublet chemotherapy (e.g. cisplatin-paclitaxel × 4, cisplatin-gemcitabine × 4)
  - **Second and further line systemic therapies**—with disease progression, consider pemetrexed (non-squamous), docetaxel, paclitaxel, albumin-bound paclitaxel, vinorelbine, vinblastine, gemcitabine, erlotinib, afatinib (EGFR+), ceritinib (ALK+), mitomycin or irinotecan

SMALL CELL LUNG CANCER

- **LIMITED STAGE, T1-2N0**—**lobectomy** followed by **adjuvant chemotherapy** or concurrent chemoradiation (if mediastinal LN involvement)
- **LIMITED STAGE, >T1-2N0**—**concurrent chemoradiation** (e.g. cisplatin-etoposide × 4) + **prophylactic cranial irradiation** if good partial/complete response
- **EXTENSIVE STAGE**—**palliative chemotherapy** (e.g. cisplatin-etoposide × 4, cisplatin-irinotecan × 4) + **prophylactic cranial irradiation** if partial/complete response. For recurrent disease after platinum-based therapy, consider

MANAGEMENT (CONT'D)

topotecan, paclitaxel, docetaxel, vinorelbine, irinotecan, oral etoposide, gemcitabine or temozolimide

NEUROENDOCRINE TUMORS

- **LOW GRADE (TYPICAL CARCINOID)**—lobectomy
- **INTERMEDIATE GRADE (ATYPICAL CARCINOID)**—lobectomy ± adjuvant chemotherapy cisplatin-etoposide (if stage II or III)
- **HIGH GRADE LARGE CELL NEUROENDOCRINE CARCINOMA**—treat as non-small cell lung cancer
- **HIGH GRADE NEUROENDOCRINE SMALL CELL CARCINOMA OR COMBINED HISTOLOGIES**—treat as small cell lung cancer

TREATMENT ISSUES

SMOKING CESSATION—for smokers of <20 pack year, the risk of developing lung cancer decreases significantly after 15 years of abstinence, but still slightly higher than non-smokers

NON-RESECTABLE DISEASE CRITERIA (stage IIIB or greater)—distant metastasis, mediastinal LN metastasis, trachea/contralateral main bronchi involvement, SVC obstruction, malignant pleural effusion, recurrent laryngeal nerve paralysis, SCLC (unless very early)

TREATMENT ISSUES (CONT'D)

CONTRAINDICATIONS TO CHEST RADIATION—significant pre-existing lung disease, cardiomyopathy, connective tissue disease (SLE, scleroderma), prior radiation to same body region, pregnancy

CONTRAINDICATIONS TO BEVACIZUMAB—squamous cell carcinoma, hemoptysis, uncontrolled cerebral metastases, non-healing wounds, uncontrolled hypertension/proteinuria, bleeding diatheses, recent trauma/surgery

PREDICTIVE FACTORS FOR EGFR INHIBITORS—clinical factors include women, Asian, never smokers, and adenocarcinoma. With all 4 factors, response rate 50% (compared to 10% normally). Pathologic predictive factors include EGFR mutation and high EGFR gene copy number

Related Topics
Dyspnea (p. 4)
Horner's Syndrome (p. 16)
SVC Syndrome (p. 253)
Solitary Pulmonary Nodule (p. 16)
Smoking Cessation (p. 480)
Superior Vena Cava Syndrome (p. 253)
Pre-Operative Assessment (p. 484)

Mesothelioma NEJM 2005 353:15

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY

- **EPITHELIOID**—tubulopapillary, glandular, or solid. 50–60%
- **SARCOMATOID**—spindle cells
- **BIPHASIC**—mixed with both epithelioid and sarcomatoid features

ASBESTOS AND MESOTHELIOMA—accounts for approximately 80% of mesothelioma. Risk of mesothelioma is higher with amphiboles/blue asbestos than chrysotile/white asbestos. Asbestos fibers may irritate the pleura, sever or pierce the mitotic spindle of cells and disrupt mitosis, induce generation of iron-related reactive oxygen species, and phosphorylate MAP kinases and ERK 1 and 2. Tumor usually starts from parietal pleura and invades locally

RISK FACTORS

- **FAMILY HISTORY**—rare
- **ENVIRONMENTAL**—asbestos, radiation

CLINICAL FEATURES

LOCOREGIONAL—pleural (pleural effusion, pleuritic chest pain, dyspnea, SVC obstruction), peritoneal (ascites, abdominal pain, bowel obstruction), pericardial (pericardial effusion, tamponade)

METASTATIC—miliary spread, liver, lung, bone, and/or adrenal lesions

CONSTITUTIONAL—weight loss, anorexia, fatigue

STAGING

TNM STAGING (7TH EDITION)

T stage

- **T1** = invasion limited to ipsilateral pleura (T1a = parietal pleura, T1b = parietal pleura with focal visceral pleura involvement)
- **T2** = invades ipsilateral visceral pleura diffusely, lung, or diaphragm
- **T3** = locally advanced potentially resectable. Tumor invades ipsilateral endothoracic

STAGING (CONT'D)

fascia, mediastinal fat, soft tissues of chest wall (solitary), pericardium (non-transmural)
- **T4** = locally advanced technically unresectable. Tumor invades contralateral pleura or lung by direct extension, soft tissues of chest wall (diffuse or multifocal), rib, any mediastinal organs, diaphragm, spine, pericardium, myocardium, brachial plexus

N STAGE
- **N1** = ipsilateral bronchopulmonary or hilar LN
- **N2** = ipsilateral mediastinal LN
- **N3** = contralateral mediastinal internal mammary, supraclavicular, or scalene LN

M STAGE
- **M1** = distant metastasis

STAGE GROUPINGS

Stage	TNM @ = any
IA	T1aN0M0
IB	T1bN0M0
II	T2N0M0
III	T1-2N1-2M0, T3N0-2M0
IV	T4N@M0, T@N3M1, T@N@M1

INVESTIGATIONS

BASIC
- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bili
- **IMAGING**—CXR, CT chest/abd, or MRI chest
- **BIOPSY**—thoracentesis (sens 33–84%, cytology is usually inadequate), thoracoscopy with pleural biopsy

SPECIAL
- **SERUM MESOTHELIN-RELATED PROTEIN** (SMRP)—sens 75–84%
- **PET SCAN**—if surgical candidate

PROGNOSTIC ISSUES

ADVERSE PROGNOSTIC FACTORS—male, poor performance status, sarcomatoid subtype, leukocytosis, anemia, thrombocytosis, advanced stage, high PET ratios

PROGNOSIS—**stage I** = 16 months median survival, ≥3 adverse prognostic factors = <6 months median survival, **stage II–IV** = 10 months median survival

MANAGEMENT

STAGE I, II (resectable disease)—**surgery** (pleurectomy/decortication, extrapleural pneumonectomy, debulking) is controversial and of questionable benefit. Pleurectomy/decortication should be the first option for patients with operable early stage disease and is an option for patients with locally advanced disease who are not candidates for extrapleural pneumonectomy. Extrapleural pneumonectomy should be considered for highly selected patients (age <55, performance status ≤1, stage I or II, epithelioid histology) and only after a good response to **neoadjuvant chemotherapy**, to be followed by **adjuvant radiation**. Otherwise, treat as unresectable disease

STAGE III, IV (unresectable disease)—palliative **chemotherapy** (cisplatin–pemetrexed with vitamin B12 and folic acid supplementation or cisplatin–gemcitabine). Second-line options include repeating cisplatin–gemcitabine, cisplatin–pemetrexed, and vinorelbine. **Pleurodesis or indwelling pleural catheters** should be considered if recurrent effusion

Thymoma and Thymic Carcinoma

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY
- **EPITHELIAL**
- **NEUROENDOCRINE**
- **GERM CELL**
- **LYMPHOID**
- **STROMAL**

CLINICAL FEATURES

LOCOREGIONAL—dyspnea, cough, chest pain, hoarseness, dysphagia, superior vena cava obstruction

CLINICAL FEATURES (CONT'D)

METASTATIC

CONSTITUTIONAL—weight loss, anorexia, fatigue

PARANEOPLASTIC—myasthenia gravis (30–50%, diplopia, ptosis, dysphagia, weakness, fatigue), pure red cell aplasia (5–15%), pure white cell aplasia, pancytopenia, hypogammaglobulinemia (recurrent infections, diarrhea), rheumatologic diseases, and endocrinopathies. Note that remission of thymoma does not necessarily correlate with improvement of paraneoplastic syndromes

STAGING

YAMAKAWA–MASAOKA TNM STAGING

T stage

- **T1** = intact capsule
- **T2** = macroscopically invades surrounding fatty tissue or mediastinal pleura, microscopically invades capsule
- **T3** = invades pericardium, great vessels, lung
- **T4** = pleural or pericardial dissemination

N stage

- **N1** = anterior mediastinal LN
- **N2** = other intrathoracic LN
- **N3** = extrathoracic LN

M stage (drop metastasis in pleural space)

- **M1** = distant metastasis

STAGE GROUPINGS

Stage	TNM @ = any	5-year survival
I	T1N0M0	95%
II	T2N0M0	85%
III	T3N0M0	70%
IVA	T4N0M0	50%
IVB	T@N1v3M0, T@N@M1	

Related Topic
Myasthenia Gravis (p. 360)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bili
- **IMAGING**—CXR, CT chest
- **BIOPSY**

MANAGEMENT

STAGE I, II, III (resectable disease)—**resection** (usually including adjacent lung parenchyma and pericardium) ± **adjuvant radiation** ± (**neo**) **adjuvant chemotherapy** [cisplatin–doxorubicin–cyclophosphamide (preferred for thymoma), carboplatin-paclitaxel (preferred for thymic carcinoma), cisplatin–etoposide]

STAGE IV (unresectable disease)—**palliative radiation** ± **palliative chemotherapy** [cisplatin–doxorubicin–cyclophosphamide (preferred for thymoma), carboplatin-paclitaxel (preferred for thymic carcinoma), cisplatin–etoposide]

TREATMENT ISSUES

INDICATIONS FOR RADIOTHERAPY—locally advanced or metastatic unresectable disease, residual disease post-resection, and complete resection of invasive thymoma or thymic carcinoma

Breast Cancer NEJM 2004 350:14

DIFFERENTIAL DIAGNOSIS OF BREAST MASS

BENIGN—cysts (obstructed collecting ducts), fibroadenoma (overgrowth of periductal stromal connective tissue within the lobules), mammary duct ectasia, intraductal papilloma, mastitis, fat necrosis

ATYPICAL HYPERPLASIA—3–5× increased risk of breast cancer

CARCINOMA IN SITU—ductal (DCIS), lobular (LCIS)

MALIGNANT—breast cancer (see below for details)

PATHOPHYSIOLOGY

CLASSIFICATION OF PRE-MALIGNANT LESIONS

- **DUCTAL CARCINOMA IN SITU** (DCIS)—precursor lesion to invasive cancer
- **LOBULAR CARCINOMA IN SITU** (LCIS)—diffuse and can be bilateral (risk of contralateral invasive breast cancer may be as high as ipsilateral disease). Marker for increased risk of development of invasive cancer (absolute risk ~1%/year of development of invasive cancer)

PATHOPHYSIOLOGY (CONT'D)

CLASSIFICATION OF MALIGNANT LESIONS

- **DUCTAL ADENOCARCINOMA**—80%
- **LOBULAR ADENOCARCINOMA**—10%, more likely to be bilateral and multicentric. Tends to metastasize later than ductal carcinoma and spreads to unusual sites such as GI tract, peritoneum, and meninges. Most are ER+ and 20–30% have E-cadherin mutations (associated with hereditary diffuse-type gastric cancer). Clinically, more difficult to detect by palpation and by mammography
- **TUBULAR, MEDULLARY, PAPILLARY, COLLOID, SPINDLE CELL, MUCINOUS**—10%, better prognosis
- **SARCOMA LIKE**—phylloides, post-radiation

PATHOPHYSIOLOGY (CONT'D)

RISK FACTORS

- **PERSONAL**—female, increased age, early age of menarche, late age of first parity, lack of breast feeding, late age of menopause, oral contraceptives (↑ risk if >4 years of use), hormone replacement, high socioeconomic status
- **FAMILY HISTORY** (10%)—affected relatives, BRCA1 and BRCA2 mutations, Li–Fraumeni syndrome, Cowden syndrome
- **ENVIRONMENTAL**—alcohol, low caloric intake, low physical activity, weight gain
- **PRIOR BREAST PATHOLOGY**—atypical hyperplasia, prior breast tumor (in situ or carcinoma)
- **GAIL MODEL**—used to estimate the risk of breast cancer in the Breast Cancer Detection and Demonstration Project. Includes age at menarche, age at first live birth, number of previous breast biopsies, presence of atypical hyperplasia in breast biopsy, and number of first-degree relatives with breast cancer

BRCA BREAST CANCERS—BRCA1 is associated with basal-like subtype and triple negative (ER negative, PR negative, Her2 negative) phenotype. BRCA2 is associated with luminal subtype. Phase II data have shown that these tumors are particularly sensitive to platinum-based chemotherapy and poly(ADP-ribose) polymerase (PARP) inhibitors due to defects in DNA homologous recombination repair from BRCA mutation

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES DOES THIS PATIENT HAVE BREAST CANCER?

PHYSICAL—the value of inspection is unproved. Palpation with clinical breast examination (CBE) includes proper positioning of the patient, use of a vertical strip pattern, proper position and movement of the fingers (pads of 2nd–4th fingers rolling motion), thoroughness of search, and spending at least 3 min per breast (sens 54%, spc 94%, LR+ 10.6, LR– 0.47)

APPROACH—"screening by both clinical breast examination and mammography is associated with decreased breast cancer mortality. Clinical breast examination alone detected between 3–45% of breast cancers that were missed by screening mammography. While clinical breast examination alone cannot rule out disease, the high specificity of certain abnormal findings significantly increases the probability of breast cancer"

CLINICAL FEATURES (CONT'D)

UPDATE—US Preventive Services Task Force and the Canadian Task Force on Preventive Health Care both discourage self-breast examination. Evidence to definitively recommend for or against routine clinical breast examination is insufficient.

JAMA 1996 282:13
The Rational Clinical Examination. McGraw-Hill, 2009

LOCOREGIONAL—breast lump (with or without pain), nipple discharge, eczema or retraction, skin erosion, erythema or edema, change in breast size, axillary adenopathy

METASTATIC—bone pain, seizure, headache, dyspnea, jaundice

CONSTITUTIONAL—fatigue, weight loss, anorexia

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin
- **IMAGING**—mammogram (15% false negative), US breast, MRI breast (for dense breasts or those with BRCA1/2 mutations)
- **BIOPSY**—needle core biopsy (FNA provides cytology only and cannot differentiate between invasive and in situ disease), excisional biopsy

SPECIAL

- **BONE SCAN AND CT CHEST/ABD/PELVIS**—if clinical stage IIIA (T3N1M0) or above
- **TUMOR MARKERS**—CA 15-3 or CA27.29 if metastatic disease

STAGING

TNM STAGING (7TH EDITION)

T stage (same clinical and pathologic staging)

- **T1** ≤ 2 cm (T1mic = microinvasion ≤0.1 cm, T1a >0.1–0.5 cm, T1b >0.5–1 cm, T1c >1–2 cm)
- **T2** > 2–5 cm
- **T3** > 5 cm
- **T4** = invades skin or chest wall (T4a = extends to chest wall, but not including pectoralis muscle; T4b = edema with peau d'orange or ulceration of the skin, or satellite skin nodules confined to the same breast; T4c = both T4a and T4b; T4d = inflammatory carcinoma)

STAGING (CONT'D)

N stage (axillary, internal mammary, supraclavicular)

- **N1**
  - **cN1** = ipsilateral mobile axillary lymph node(s)
  - **pN1mi** = micrometastasis 0.2–2 mm
  - **pN1a** = 1–3 axillary lymph node(s)
  - **pN1b** = internal mammary lymph nodes with microscopic disease detected by SLND but not clinically apparent
  - **pN1c** = N1a and N1b
- **N2**
  - **cN2a** = ipsilateral fixed/matted axillary lymph node(s)
  - **cN2b** = ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node
  - **pN2a** = 4–9 axillary lymph nodes
  - **pN2b** = ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node
- **N3**
  - **cN3a** = ipsilateral infraclavicular lymph node(s)
  - **cN3b** = ipsilateral internal mammary and axillary lymph node(s)
  - **cN3c** = ipsilateral supraclavicular lymph node(s)
  - **pN3a** = 10 or more axillary lymph nodes or metastasis to the infraclavicular lymph nodes
  - **pN3b** = metastasis in clinically apparent ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary node, or in >3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent
  - **pN3c** = ipsilateral supraclavicular lymph node

M stage (lungs, liver, bones, brain)

- **M1** = distant metastasis

STAGE GROUPINGS

Stage	TNM @ = any	5-Year survival
I	T1N0M0, T0-1N1miM0	100%
IIA	T0-1N1M0, T2N0M0	90%
IIB	T2N1M0, T3N0M0	80%
IIIA	T0-2N2M0, T3N1-2M0	70%
IIIB	T4N0-2M0	50%
IIIC	T@N3M0	40%
IV	T@N@M1	20%

DIAGNOSTIC AND PROGNOSTIC ISSUES

MAMMOGRAPHIC FINDINGS OF BREAST CANCER—spiculated, crab-like, puckering lesions, architectural distortion, clustered microcalcifications

SCREENING—if average risk population, mammogram q2 years starting age 50 (may begin annual mammogram screening earlier at age 40); if high risk, annual clinical breast examination and mammography (starting 5-10 years younger than age of onset for youngest proband if strong family history)

POOR PROGNOSTIC FACTORS—young age, advanced stage (especially nodal status and tumor size), high grade, Her2/neu+, ER–, PR–, lymphatic/vascular invasion

MANAGEMENT

DCIS

- **RESECTION**—breast-conserving surgery plus adjuvant radiation, or mastectomy
- **ADJUVANT HORMONAL**—tamoxifen may be considered after breast-conserving surgery for selected individuals if ER/PR positive

LCIS

- **RESECTION**—observation, breast-conserving surgery or bilateral mastectomy for selected individuals
- **HORMONAL**—tamoxifen or raloxifene may be used for prevention of invasive breast cancer in selected individuals

STAGE I AND II

1. **RESECTION**—breast-conserving surgery or mastectomy, plus sentinel node biopsy. Axillary lymph node dissection if clinically node positive and biopsy proven. If sentinel lymph node positive, proceed to axillary dissection
2. **ADJUVANT SYSTEMIC THERAPY**—taxane ± anthracycline ± trastuzumab
3. **ADJUVANT RADIATION**—always give adjuvant radiation after breast-conserving surgery. Adjuvant radiation should be considered after mastectomy if large tumor, skin involvement, muscle involvement, positive nodes, positive margins, or lymphovascular invasion
4. **ADJUVANT HORMONAL THERAPY**—give if ER/PR positive

STAGE III

1. **NEOADJUVANT/ADJUVANT SYSTEMIC THERAPY**—taxane ± anthracycline ± trastuzumab ± pertuzumab (only approved in neoadjuvant setting, not adjuvant). Adjuvant therapy if tumor resectable upfront

MANAGEMENT (CONT'D)

2. **RESECTION**—breast-conserving surgery or mastectomy, plus axillary lymph node dissection
3. **ADJUVANT RADIATION**—almost always given for stage III disease
4. **ADJUVANT HORMONAL THERAPY**—give if ER/PR positive

STAGE IV

1. **ER/PR–, HER2– (TRIPLE NEGATIVE) DISEASE**—chemotherapy choices include anthracyclines (doxorubicin, pegylated liposomal doxorubicin), taxanes (paclitaxel, docetaxel, albumin-bound paclitaxel), anti-metabolites (gemcitabine, capecitabine), microtubule inhibitors (vinorelbine, eribulin, ixabepilone), platinums (carboplatin, cisplatin), or various combinations (e.g. doxorubicin-cyclophosphamide, gemcitabine-carboplatin)
2. **ER/PR+, HER2- DISEASE**—if not rapidly progressive/symptomatic and no significant visceral involvement, consider endocrine therapy such as tamoxifen, aromatase inhibitors, or fulvestrant. In premenopausal women, the use of aromatase inhibitors and fluvestrant require either oophorectomy or LHRH agonists. Otherwise, consider single agent or combination chemotherapy (see triple negative disease)
3. **ER/PR+, HER2+ DISEASE**—if not rapidly progressive/symptomatic and no significant visceral involvement, consider HER2-directed therapy in combination with endocrine therapy. Otherwise, pertuzumab-trastuzumab-docetaxel (or paclitaxel) is first line therapy. Other options include ado-trastuzumab emtansine (T-DM1), lapatinib-based combinations (with capectiabine or trastuzumab), or single agent or combination chemotherapy (see triple negative disease) plus trastuzumab
4. **ER/PR-, HER2+ DISEASE**—pertuzumab-trastuzumab-docetaxel (or paclitaxel) is first line therapy. Other options include ado-trastuzumab emtansine (T-DM1), lapatinib-based combinations (with capectiabine or trastuzumab), or single agent or combination chemotherapy (see triple negative disease) plus trastuzumab
5. **PALLIATIVE RADIATION**—for symptomatic control of localized disease (e.g. bone metastasis, painful skin lesions)
6. **BONE METASTASES**—if bone metastasis, *pamidronate* 90 mg IV over 2 h q4w, or *zoledronate* 4 mg IV over 15 min q4w (dose based on creatinine clearance) for up to 2 years. *Denosumab* 120 mg SC q4wk represents an alternative to bisphosphonates

MANAGEMENT (CONT'D)

LOCAL RECURRENCE—biopsy to try to distinguish recurrence from new primary, metastatic workup. If isolated local recurrence, resection/completion mastectomy ± radiation. Hormonal and/or chemotherapy may also be considered

Related Topics
BRCA Mutations (p. 244)
Cancer Screening (p. 240)

BREAST SURGERY OVERVIEW

COMPLETE SURGERY—modified radical mastectomy, radical mastectomy. Indications for mastectomy include multicentric disease, diffuse malignant appearing microcalcifications on mammography, prior breast radiation, and pregnancy. Relative indications include large tumor (>5 cm), connective tissue disease (radiation contraindicated), and patient preference. Poorer cosmesis compared to breast-conserving surgery

BREAST CONSERVING SURGERY—excisional biopsy, lumpectomy, partial mastectomy, quadrantectomy, wide local excision

SURGICAL MARGIN—positive margin is defined as tumor touching ink and would require re-excision

AXILLARY LYMPH NODE DISSECTION (ALND)—used in all invasive carcinoma. May be avoided if sentinel lymph node negative

SENTINEL LYMPH NODE BIOPSY—indicated for clinically node negative tumors. Contraindications include locally advanced breast cancer, any palpable lymph nodes, multifocal cancers, previous disruptive breast procedures, and adverse reactions to dyes. Proceed to ALND if positive nodes or unable to identify sentinel node

HORMONAL THERAPY OVERVIEW

HORMONAL REGIMENS

- **OVARIAN ABLATION** (premenopausal only)—oophorectomy, radiation, or LHRH agonists (*goserelin* 3.6 mg IM every month, leuprolide). Consider combining with tamoxifen (in adjuvant or metastatic settings) or aromatase inhibitors (in metastatic setting only) for maximal effect
- **SELECTIVE ESTROGEN RECEPTOR MODULATORS** (premenopausal or postmenopausal)—*tamoxifen* 20 mg PO daily. Side effects include hot flashes,

HORMONAL THERAPY OVERVIEW (CONT'D)

mood swings, vaginal discharge, thromboembolism, and endometrial cancer. Protective effect with bones and lipids

- **AROMATASE INHIBITORS** (for postmenopausal women or premenopausal women after ovarian ablation as suppress peripheral estrone production only)—inhibit aromatase, an enzyme in skin, adipose tissue, and breast that converts androstenedione (from the adrenals) to estrone and estradiol. **Steroidal** (*exemestane* 25 mg PO daily), **non-steroidal** (*letrozole* 2.5 mg PO daily, *anastrozole* 1 mg PO daily). Side effects include hot flashes, mood swings, vaginal dryness, myalgia/arthralgia, headache, osteoporosis, dyslipidemia, weight gain, and potentially CAD
- **ANTIESTROGEN**—*fulvestrant* 500 mg IM loading dose on days 1 and 15, then 500 mg monthly
- **OTHERS**—*megestrol acetate* 160 mg PO daily, methyltestosterone

PREDICTIVE FACTORS FOR HORMONAL THERAPY—degree of response to tamoxifen varies (ER + PR+ > ER + PR– > ER–PR+ > ER–PR–). Hormonal therapy is not given to patients with ER- and PR- cancers. Her2+ may also interfere with ER pathways

APPROACH IN THE ADJUVANT SETTING—for premenopausal women, consider tamoxifen × 5-10 years. For postmenopausal women, consider one of the following: anastrozole × 5 years, letrozole × 5 years, tamoxifen × 2–3 years followed by exemestane or anastrozole to complete 5 years of adjuvant hormonal therapy, tamoxifen × 5 years followed by letrozole × 5 years, or tamoxifen × 10 years. Consider aromatase inhibitors as first hormonal agent if >10% risk of relapse in first 2 years (e.g. ≥4 positive nodes, low ER or grade 3 disease)

APPROACH IN THE METASTATIC SETTING—patients with slowly progressive disease, no visceral involvement, and minimal symptoms may be best served with a trial of endocrine therapy. For premenopausal women, consider tamoxifen or ovarian ablation + tamoxifen → aromatase inhibitor 1 → aromatase inhibitor 2 → fulvestrant → megestrol. For postmenopausal women, aromatase inhibitor 1 → tamoxifen → aromatase inhibitor 2 → fulvestrant → megestrol. Time to progression is 8 months with tamoxifen and 10 months with aromatase inhibitors

NEOADJUVANT/ADJUVANT CHEMOTHERAPY OVERVIEW

WHO SHOULD GET ADJUVANT CHEMOTHERAPY: THE NCCN GUIDELINE

- **ALL HISTOLOGIC SUBTYPES EXCEPT TUBULAR OR COLLOID CANCERS**—adjuvant chemotherapy should be given if ≥1 cm or node positive. Consider chemotherapy if 0.6–1 cm and high grade or lymphovascular invasion. Add trastuzumab if Her2/neu positive
- **TUBULAR OR COLLOID CANCERS**—adjuvant chemotherapy should be given if ≥3 cm or node positive. Consider chemotherapy if 1–2.9 cm

ONCOTYPE DX—the 21-gene recurrence score is a validated prognostic assay. It is applicable only to pathologically node-negative, hormone receptor-positive, and Her2-negative tumors to help with the decision of adjuvant chemotherapy. A score of <18, 18-30, and >31 defines the low (no chemotherapy recommended), intermediate (chemotherapy should be considered) and high risk (chemotherapy recommended) groups, respectively

ADJUVANT! ONLINE (www.adjuvantonline.com)—this web-based program determines both recurrence risk and probability of survival with the use of adjuvant chemotherapy. However, it does not account for Her2 status

NEOADJUVANT/ADJUVANT REGIMENS

- **FIRST GENERATION**—CMF PO, AC × 4, FEC50 × 6
- **SECOND GENERATION**—CAF × 6, FAC × 6, CEF × 6, FEC100 × 6, AC × 4 + D × 4, DC × 4
- **THIRD GENERATION**—DAC × 6, FEC100 × 3 + D × 3, AC × 4 + T × 4 (dose dense), FEC × 4 + T × 8
- **NOTE**—for Her2 positive add trastuzumab plus pertuzumab to neoadjuvant regimens as clinically indicated, and trastuzumab alone to adjuvant regimens. Abbreviations: A = doxorubicin, C = cyclophosphamide, D = docetaxel, E = epirubicin, F = 5-fluorouracil, M = methotrexate, T = paclitaxel

NEOADJUVANT/ADJUVANT CHEMOTHERAPY OVERVIEW (CONT'D)

ESTIMATED BENEFITS OF ADJUVANT CHEMOTHERAPY

RELATIVE RISK REDUCTION FOR MORTALITY

	Postmenopausal	Premenopausal
1st gen.	8% ER+, 15% ER–	30%
2nd gen.	26% ER+, 32% ER–	44%
3rd gen.	40% ER+, 45% ER–	55%

RELATIVE RISK REDUCTION FOR RECURRENCE

	Postmenopausal	Premenopausal
1st gen.	12% ER+, 23% ER–	37%
2nd gen.	30% ER+, 38% ER–	50%
3rd gen.	43% ER+, 50% ER–	59%

ADVERSE EFFECTS OF ADJUVANT CHEMOTHERAPY

- **ALOPECIA**—anthracycline or taxane regimens (100%), CMF (50%)
- **FEBRILE NEUTROPENIA**—DAC (40%) and dose dense regimens require GCSF. CEF > FEC; FAC > FEC; ACT > AC/CMF

NEOADJUVANT/ADJUVANT CHEMOTHERAPY OVERVIEW (CONT'D)

- **NAUSEA AND VOMITING**—CMF > anthracyclines
- **OTHER ACUTE SIDE EFFECTS**—fatigue and weight gain. With taxanes, may experience myalgia, arthralgia, and neuropathy (motor, sensory)
- **PREMATURE OVARIAN FAILURE**—CMF > CEF/FEC > AC; DAC > FAC
- **OTHER LONG-TERM SIDE EFFECTS**—cardiotoxicity (dose dependent and increases with age, ~1% with anthracycline doses used in adjuvant regimens), secondary cancers (AML, MDS with alkylating agents, ~1–2% depending on regimen)

PREDICTIVE FACTORS FOR ADJUVANT CHEMOTHERAPY BENEFIT—younger age, high grade, ER negative, Her2 positive (possibly for anthracycline and taxane-based regimens)

APPROACH IN THE ADJUVANT SETTING—chemotherapy usually starts 4–10 weeks after surgery. Consider anthracycline followed by taxane (e.g. AC × 4 and weekly T × 12) for intermediate/high risk or node-positive breast cancer; anthracycline ± taxane + trastuzumab for Her2 positive breast cancer; CMF or DC if anthracycline contraindicated or preexisting heart disease

ADVANTAGES AND DISADVANTAGES OF NEOADJUVANT AND ADJUVANT THERAPY

Neoadjuvant	Adjuvant
Clinical staging is less accurate	Accurate pathological staging
Pathological confirmation of chemotherapy efficacy "in vivo response"	No confirmation
Definitive treatment delayed	Definitive treatment early on
Reduced tumor improves local control	No reduction of tumor before surgery
Surgery refusal in patients with complete response	All patients undergo surgery
Timely application of chemotherapy	Delayed or no chemotherapy in patients with post-op complications
Better performance status allowing aggressive therapy	Impaired performance status post-op
Intact blood/lymph vessels allowing optimal drug concentrations	Impaired blood/lymph vessel supply in pelvis

PALLIATIVE CHEMOTHERAPY OVERVIEW

PALLIATIVE REGIMENS—single agent choices include anthracyclines (doxorubicin, pegylated liposomal doxorubicin), taxanes (paclitaxel, docetaxel, albumin-bound paclitaxel), antimetabolites (gemcitabine, capecitabine), microtubule inhibitors (vinorelbine, eribulin, ixabepilone), and platinums (carboplatin, cisplaitin). Doublet regimens include doxorubicin-cyclophosphamide, carboplatin-gemcitabine, doxorubicin-paclitaxel, capecitabine-docetaxel, docetaxel-gemcitabine, and paclitaxel-gemcitabine

APPROACH IN THE METASTATIC SETTING—patients with rapidly growing disease, especially involvement of visceral organs such as lung or liver may benefit more from chemotherapy compared to hormonal therapy due to a more rapid response. The choice of first line palliative chemotherapy depends on prior adjuvant chemotherapy, disease-free interval, patient's performance status, and willingness/ability to tolerate side effects. Doublet regimens are associated with higher response rate, while single agents are better tolerated and are particularly appropriate for patients who are elderly or have poor performance status. Consider doublet regimens in patients that need a rapid response to relieve tumor-related symptoms. At eventual disease progression, change chemotherapy to non-cross-resistance single agents

BIOLOGICAL THERAPY OVERVIEW

HER2/NEU STATUS—15–20% positive. Her2 positivity is a poor prognostic factor, but predicts response to trastuzumab, pertuzumab, ado-trastuzumab emtansine (T-DM1), and lapatinib

APPROACH—Her2 positive disease should be treated with chemotherapy plus trastuzumab in the adjuvant/neoadjuvant settings. Do not give concomitantly with anthracyclines. In the metastatic setting, give chemotherapy and then maintenance trastuzumab until progression

ADVERSE EFFECTS—infusion reactions (40%, usually with first administration), cardiotoxicity, and pulmonary (rare)

DISTINGUISHING FEATURES BETWEEN CARDIOTOXICITY DUE TO ANTHRACYCLINE AND TRASTUZUMAB

	Anthracycline	Trastuzumab
Mechanism	Lipid peroxidation and vacuolation → myocyte fibrosis	Unknown
Structural damage	Present	Not seen
Cardiomyopathy	Dilated	Dilated
Dose dependent	Yes	No
Prevention	Dexrazoxone Weekly Treatment Liposomal Doxorubicin Limit dose	None
Treatment	Stop therapy Cannot give more	Stop therapy May restart
Course	Irreversible	Reversible

MANAGEMENT OF BRAIN METASTASES

APPROACH—steroids, resection plus radiation, or radiation alone if resection not possible. Principles are similar for CNS recurrence

- **SURGERY**—consider resection if solitary lesion or primary lesion causing neurological complications. Surgery plus radiation is associated with better overall survival than radiation alone for eligible candidates (10 vs. 6 months)

MANAGEMENT OF BRAIN METASTASES (CONT'D)

- **RADIATION**—may be re-irradiated if over 1 year from first whole brain radiation
- **STEREOTACTIC RADIATION**—less generalized toxicity. If <3 lesions and all <3 cm [<1.2 in.]
- **CHEMOTHERAPY**—limited role with high-dose methotrexate and possibly capecitabine

Esophageal Cancer

NEJM 2003 349:23

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY

- **ADENOCARCINOMA**—75% in distal esophagus
- **SQUAMOUS**—evenly distributed between upper, middle, and lower thirds of esophagus
- **MELANOMA**
- **LEIOMYOSARCOMA**
- **LYMPHOMA**
- **CARCINOID**

RISK FACTORS

	Squamous	Adeno
Barrett's esophagus	–	>8×
Reflux symptoms	–	4–8×
Obesity	–	2–4×
Smoking	4–8×	2–4×
Alcohol Use	4–8×	–
Caustic injury to esophagus	>8×	–
Achalasia	4–8×	–
Poverty	2–4×	–
History of H&N cancer	>8×	–
History of breast cancer with radiation	4–8×	4–8×
Plummer–Vinson syndrome	>8×	–
Non-epidermolytic palmoplantar keratoderma	>8×	–
Frequent hot beverages	<2×	–

CLINICAL FEATURES

LOCAL—dysphagia (74%), odynophagia (17%), upper GI bleed, epigastric pain

PATHOPHYSIOLOGY (CONT'D)

REGIONAL—dyspnea, cough, hoarseness, pain (retrosternal, back, RUQ)

METASTATIC—Virchow's node, hepatomegaly, pleural effusion

CONSTITUTIONAL—anorexia, fatigue, weight loss

Related Topics
Barrett's Esophagus (p. 127)
Esophageal Dysphagia (p. 124)
Gastric Cancer (p. 217)

STAGING

TNM STAGING (7TH EDITION)

T stage

- **T1** = invades lamina propria, muscularis mucosa, or submucosa
- **T2** = invades muscularis propria
- **T3** = invades adventitia
- **T4** = invades into adjacent structures (pleura, pericardium, diaphragm, aorta, vertebral body, trachea, mediastinum)

N stage (cervical paraesophageal, right recurrent laryngeal, left paratracheal, upper and lower paraesophageal, infraaortic, infracarinal and lower posterior mediastinal regions)

- **N1** = 1-2 regional lymph nodes
- **N2** = 3-6 regional lymph nodes
- **N3** = 7 or more regional lymph nodes

M stage (spreads rapidly and early. Over 50% unresectable/metastatic disease at presentation)

- **M1** = distant metastasis

STAGING (CONT'D)

STAGE GROUPINGS

Stage	Squamous TNM @ = any	Adeno TNM @ = any	5-year survival
0	TisN0M0	TisN0M0	>95%
IA	T1N0M0G1	T1N0M0G1-2	50–80%
IB	T1N0M0G2-3	T1N0M0G3	
	T2-3N0M0G1 lower eso.	T2N0M0G1-2	
IIA	T2-3N0M0G1 upper/mid	T2N0M0G3	30–40%
	T2-3N0M0G2-3 lower eso.		
IIB	T2-3N0M0G2-3 upper/mid	T3N0M0G@	10–30%
	T1-2N1M0G@	T1-2N1M0G@	
IIIA	T1-2N2M0G@	T1-2N2M0G@	10–15%
	T3N1M0G@	T3N1M0G@	
	T4aN0M0G@	T4aN0M0G@	
IIIB	T3N2M0G@	T3N2M0G@	
IIIC	T4aN1-2M0G@	T4aN1-2M0G@	
	T4bN@M0G@	T4bN@M0G@	
	T@N3M0G@	T@N3M0G@	
IV	T@N@M1G@	T@N@M1G@	<5%

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, lipase, CEA
- **IMAGING**—CXR, barium swallow, CT chest and abd, endoscopic US (excellent for staging), PET scan (preoperative workup)
- **BIOPSY**—gastroscopy ± laparoscopy

DIAGNOSTIC AND PROGNOSTIC ISSUES

SCREENING (for Barrett's)—consider screening gastroscopy in patients with risk factors (age ≥50, male, white race, chronic GERD >5 years, hiatal hernia, high BMI or intra-abdominal fat distribution, ±tobacco use, ±nocturnal reflux)

SURVEILLANCE (for Barrett's)—endoscopic surveillance with four-quadrant biopsies q3-5 years (if no dysplasia on biopsy), q6-12 months (low-grade dysplasia), q3 months (high-grade dysplasia without eradication therapy)

POOR PROGNOSTIC FACTORS—weight loss >10%, dysphagia, large tumors, advanced age, lymphatic micrometastases

MANAGEMENT

NUTRITIONAL SUPPORT—dietician consult. Consider supplemental feeding if significant weight loss, but only if benefits greater than risk

RESECTABLE

- **SURGICAL RESECTION** (right transthoracic approach, transhiatal approach)—surgery only for T1N0 disease. Add preoperative chemoradiation (weekly carboplatin-paclitaxel, or 5-fluorouracil plus cisplatin, 4140–5040 cGy) if T2-4 or N+ disease. Endoscopic resection is a reasonable alternative to surgery, particularly for older individuals, medically inoperable patients

MANAGEMENT (CONT'D)

- **DEFINITIVE CHEMORADIATION**—weekly carboplatin-paclitaxel, or 5-fluorouracil plus cisplatin, 4140-5040 cGy may be a reasonable alternative to surgery, particularly for older individuals, medically inoperable patients, and cervical esophageal carcinoma (difficult resection)
- **MAGIC REGIMEN**—ECF × 3 (E = epirubicin, C = cisplatin, F = infusional 5-fluorouracil) + **surgical resection** followed by ECF × 3 similar to treatment for gastric cancer if GE junction involved, good performance status, and not dysphagic
- **IMMEDIATE RESECTION FOLLOWED BY POSTOPERATIVE CHEMORADIATION**—if unsuitable for preoperative therapy

LOCALLY ADVANCED, UNRESECTABLE (T3–4, N1, 65%, median survival 12–14 months)

- **ADENOCARCINOMA**—primary chemoradiation if localized. See also metastatic, unresectable cancer
- **SQUAMOUS CELL CARCINOMA**—chemoradiation (weekly carboplatin-paclitaxel, or 5-fluorouracil plus cisplatin, 4140-5040 cGy). Palliative surgical resection may be considered for selected patients (increased local control), although squamous cell carcinomas are very sensitive to chemoradiation, and thus surgery may not be needed

MANAGEMENT (CONT'D)

METASTATIC, UNRESECTABLE (M1, 15%, median survival 9–12 months)

- **PALLIATIVE CHEMOTHERAPY**—similar to gastric cancer. Standard regimens include ECF, DCF (C = cisplatin, D = docetaxel, E = epirubicin, F = 5-fluorouracil), ECX and EOX, EOF (X = capecitabine, O = oxaliplatin). For patients with poor performance status, consider CF, FOLFOX (5-fluorouracil–leucovorin–oxaliplatin), FOLFIRI (5-fluorouracil–leucovorin–irinotecan), or 5-fluorouracil or irinotecan alone. No standard for second line, which may include FOLFIRI, irinotecan alone, or taxane alone. Response rate 10–30% for single agents and 30–50% for combination therapy
- **PALLIATIVE RADIATION**—brachytherapy, external beam radiation
- **PALLIATIVE PROCEDURES**—dilatation and endoluminal stent if obstruction, phototherapy, G-tube insertion

TREATMENT ISSUES

FOLLOW-UP—no agreed upon surveillance program. Clinical assessment every 3 months during the first year, then every 6 months for a total of 5 years. Endoscopy as clinically indicated

Gastric Cancer

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY

- **ADENOCARCINOMA** (95%)—diffuse, intestinal, or mixed type
- **LEIOMYOSARCOMA** (5%)
- **LYMPHOMA**—mucosal-associated lymphoma
- **CARCINOID**
- **GI STROMAL**

PATHOLOGIC SUBTYPES

	Diffuse type	Intestinal type
Location	Proximal	Distal
Age of onset	Younger	Older
Gender	F > M	M > F
Risk factors	Hereditary	Endemic
H. pylori	32%	89%
Metastasis	Peritoneal	Hepatic
Outcome	Worse	Better

LINITIS PLASTICA (15%)—diffuse disease involving the entire stomach. Very poor prognosis; slightly better with superficial/expansive type (5–10%)

LOCATION—35% proximal, 25% body, 40% distal

RISK FACTORS

- **ETHNICITY**—Asian origin (Japanese and Chinese)
- **FAMILY HISTORY**—affected relatives (L), HNPCC, FAP, Li–Fraumeni, Peutz–Jeghers syndrome, hereditary diffuse gastric cancer
- **ENVIRONMENTAL**—nitrite consumption (pickled, salted, and cured foods), alcohol (U), smoking (U), lower socioeconomic status (L)
- **DISEASES**—*H. pylori* (L), EBV, hiatus hernia (U), pernicious anemia (3–18×), chronic gastritis, gastric polyps, previous partial gastrectomy where U = upper stomach, L = lower stomach

CLINICAL FEATURES

LOCOREGIONAL—epigastric pain, nausea and vomiting, dysphagia, upper GI bleed (melena, hematemesis), anemia, abdominal mass

METASTATIC—hepatomegaly, Virchow's node (left supraclavicular LN), Irish's node (left axillary LN), dyspnea, sister Mary Joseph nodule (umbilicus), Krukenberg tumor (ovaries)

CONSTITUTIONAL—anorexia, fatigue, weight loss

PARANEOPLASTIC—acanthosis nigricans, seborrheic keratosis (Leser–Trelat sign), inflammatory myositis, circinate erythema, cerebellar ataxia, thromboembolism, Cushing's, carcinoid

STAGING

TNM STAGING (7TH EDITION)

T stage

- **T1** = invades lamina propria, muscularis mucosa or submucosa
- **T2** = invades muscularis propria
- **T3** = penetrates subserosa without invasion of serosa (visceral peritoneum)
- **T4** = invades serosa (visceral peritoneum) or adjacent structures (esophagus, small bowel, transverse colon, spleen, liver, pancreas, adrenal gland, kidney, diaphragm, abdominal wall, retroperitoneum)

N stage (around stomach and along left gastric, common hepatic, splenic, celiac arteries)

- **N1** = 1-2 LN
- **N2** = 3-6 LN
- **N3** = 7 or more LN

M stage (liver, lung, peritoneum, left supraclavicular LN, left axillary LN, umbilicus, ovary)

- **M1** = distant metastasis

STAGING (CONT'D)

STAGE GROUPING

Stage	TNM @ = any	Freq	5-year survival
IA	T1N0M0	10%	78%
IB	T2N0M0, T1N1M0		58%
IIA	T3N0M0, T2N1M0, T1N2M0	20%	34%
IIB	T4aN0M0, T3N1M0, T2N2M0, T1N3M0		
IIIA	T4aN1M0, T3N2M0, T2N3M0	40%	8–20%
IIIB	T4bN0-1M0, T4aN2M0, T3N3M0		
IIIC	T4bN2-3M0, T4aN3M0		
IV	T@N@M1	30%	7%

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, lipase, CEA, CA 19–9
- **IMAGING**—CXR, barium swallow, endoscopic US, CT abd, US abd, PET/CT
- **BIOPSY**—gastroscopy (biopsy with *H. pylori* testing), laparotomy

DIAGNOSTIC AND PROGNOSTIC ISSUES

SCREENING—screening program in Japan may have contributed to the improved survival in that population through early detection of resectable gastric cancer. Not recommended outside countries with a high gastric cancer burden

POOR PROGNOSTIC FACTORS—advanced stage, high grade, proximal location

Related Topics
Dyspepsia (p. 125)
Leser-Trelat Sign (p. 418)
MALT (p. 197)
Melena (p. 131)

MANAGEMENT

STAGE IA—gastrectomy (total or subtotal) with **D2 dissection**

STAGE IB, II, III

- **OPTION 1—neoadjuvant ECF×3** (epirubicin, cisplatin, infusional 5-fluorouracil) + **surgery + adjuvant ECF×3**; 43% of patients able to complete treatment
- **OPTION 2—gastrectomy** (total or subtotal) with D2 dissection + **adjuvant chemoradiation** (5-fluorouracil)
- **INSUFFICIENT EVIDENCE**—adjuvant radiation alone, adjuvant chemotherapy alone, and neoadjuvant radiation

STAGE IV (T1-4N1–3M0)—same treatment approach as stage III if resectable disease. Otherwise, same treatment approach as metastatic disease

STAGE IV (M1, MEDIAN SURVIVAL 10 MONTHS)

- **PALLIATIVE CHEMOTHERAPY**—standard regimens include ECF (E = epirubicin, C = cisplatin, F = infusional 5-fluorouracil), DCF (D = docetaxel, C = cisplatin, F = 5-fluorouracil), ECX, EOX, EOF (X = capecitabine, O = oxaliplatin). For patients with poor performance status, consider CF, FOLFOX (5-fluorouracil–leucovorin–oxaliplatin), FOLFIRI (5-fluorouracil–leucovorin–irinotecan), 5-fluorouracil alone, or irinotecan alone. Second line therapy may include paclitaxel plus ramucirumab, FOLFIRI, irinotecan alone, or taxane alone. Findings from the TOGA trial demonstrate improved survival with the addition of trastuzumab to chemotherapy in HER2-positive gastric cancer (positivity rate 15–20%)
- **PALLIATIVE RADIATION**—for bony metastasis or bleeding tumors
- **PALLIATIVE SURGERY**—gastrojejunostomy, partial gastrectomy to bypass obstruction

TREATMENT ISSUES

VITAMIN B12 DEFICIENCY—may develop after a few years in patients who received subtotal or total gastrectomy

LYMPH NODE RESECTION

- **D1 dissection**—removal of the stomach and less and greater omentum with the associated N1 perigastric lymph nodes
- **D2 dissection**—D1 dissection, plus removal of N2 lymph nodes, including a splenectomy and distal pancreatectomy

FOLLOW-UP—no agreed upon surveillance program. q3month for first year, then every 6 months for a total of 5 years. Endoscopy as clinically indicated

Colorectal Cancer

NEJM 2005 352:5

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY

- **ADENOCARCINOMA**—mucinous subtype, signet-ring cells, adenosquamous, medullary
- **CARCINOID**—mostly involving appendix and rectum, less malignant
- **RARE**—squamous cell, small cell, undifferentiated
- **ADENOMATOUS POLYP**—pre-malignant

RISK FACTORS

- **PERSONAL**—age
- **FAMILY HISTORY**—affected relatives (2×), hereditary nonpolyposis colorectal cancer/Lynch syndrome (HNPCC: mutation in MSH-2, MLH-1, PMS-1, PMS-2, or MSH-6 genes responsible for mismatch repair, 6% of all colon cancers), familial adenomatous polyposis (FAP: 1% of all colon cancers related to mutation in APC gene, all affected will have colon cancer by age 40), Peutz–Jeghers syndrome, juvenile polyposis, Gardner's syndrome, Turcot's syndrome, flat adenoma syndrome
- **ENVIRONMENTAL**—decreased fiber intake
- **DISEASES**—prior colon cancer, polyps, ovarian, breast, endometrial cancer, Crohn's, ulcerative colitis (1%/year after 10 years), diabetes, obesity

LOCATION—50% rectosigmoid, 18% descending colon, 11% transverse colon, 20% in the ascending colon and cecum

DISTINGUISHING FEATURES BETWEEN COLON AND RECTAL CANCER

	Colon cancer	Rectal cancer
Frequency	2/3	1/3
Location	>12 cm [>4.7 in.] from anal verge or above peritoneal reflection	<12 cm [<4.7 in.] from anal verge or below peritoneal reflection
Metastasis	Liver	Liver and lung
Adjuvant treatments	Chemo	RT and chemo

MOLECULAR SEQUENCE FOR DEVELOPMENT OF COLON CANCER—the Vogelstein model of carcinogenesis developed based on analysis of FAP lesions. Normal epithelium → loss of 5q (e.g. APC, β-catenin) over decades → adenoma development → loss of 18q (e.g. k-ras) over 2–5 years → late adenoma → loss of 17p (e.g. p53) over 2–5 years → early cancer → loss of 8p → late cancer

MICROSATELLITE INSTABILITY (MSI)—may either be inherited as in HNPCC or spontaneous (15% of sporadic colon cancers). MSI is characterized by a decreased response to 5-fluorouracil-based adjuvant chemotherapy but improved prognosis

K-RAS MUTATION—about 40% of colon cancer has mutation in KRAS, which plays a key role in signal transduction downstream of EGFR. Tumors with wildtype K-ras have been shown to be more responsive to EGFR-based therapy (panitumumab, cetuximab) compared to mutant. This makes biologic sense as a mutated KRAS could continue to activate cell proliferation despite inhibition of EGFR

CLINICAL FEATURES

LOCOREGIONAL—bowel habit Δ, hematochezia, paradoxical diarrhea, tenesmus, abdominal pain, iron deficiency anemia

METASTATIC—RUQ pain, dyspnea

CONSTITUTIONAL—weight loss, anorexia, fatigue

OTHER—*Streptococcus bovis* bacteremia and *Clostridium septicum* sepsis; colorectal cancer in 16–32% of patients with *S. bovis* bacteremia

STAGING

TNM STAGING (7TH EDITION)

T stage

- **T1** = invades submucosa
- **T2** = invades muscularis propria
- **T3** = invades subserosa or non-peritonealized pericolic tissues
- **T4** = perforation of visceral peritoneum or directly invades into adjacent structure (bowel, bladder, uterus, pelvic wall)

N stage (mesenteric → supraclavicular)

- **N1** = 1–3 LN
  - N1a = 1 LN
  - N1b = 2–3 LN
  - N1c = tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
- **N2** = ≥4 LN
  - N2a = 4–6 LN
  - N2b = 7 LN

STAGING (CONT'D)

M stage (liver, lung, bone, brain)
- **M1** = distant metastasis

STAGE GROUPING

Stage	TNM @ = any	Freq	5-year survival
I	T1-2N0M0	15%	77%
IIA	T3N0M0	20%	67%
IIB	T4aN0M0		61%
IIC	T4bN0M0		46%
IIIA	T1-2N1M0, T1N2aM0	40%	65–74%
IIIB	T3-4aN1M0, T2-3N2aM0, T1-2N2bM0		52–58%
IIIC	T4aN2aM0, T3-4aN2bM0, T4bN1-2M0		13–42%
IV	T@N@M1	25%	<10%

INVESTIGATIONS

BASIC
- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, lipase, CEA, CA19–9
- **IMAGING**—barium enema, CT abd, CXR, MRI, and endorectal US in rectal cancer
- **BIOPSY**—colonoscopy with biopsy, laparoscopy, laparotomy

MANAGEMENT OF COLON CANCER

STAGE I—**surgical resection** only

STAGE II—**surgical resection. Adjuvant chemotherapy** (capecitabine, 5-fluorouracil–leucovorin, consider FOLFOX if high risk) may be given if adverse prognostic features (T4, perforation, obstruction, poorly differentiated, signet ring cell and mucinous histology, lymphovascular invasion, inadequate LN sampling <12)

STAGE III—**surgical resection** + **adjuvant chemotherapy** (FOLFOX is the first choice. Other possibilities include capecitabine, 5–fluorouracil-leucovorin, infusional 5-fluorouracil if patient is not fit or has contraindications to oxaliplatin)

STAGE IV—if metastasis limited to liver and potentially resectable, consider liver **resection** plus perioperative chemotherapy. **Radiofrequency ablation** could be considered if patient unfit for surgery. If non-resectable disease, **palliative chemotherapy** (FOLFIRI ± bevacizumab, FOLFOX ± bevacizumab, or regorafenib. capecitabine or 5-fluorouracil/LV if patient unfit. Raltitrexed if 5-fluorouracil intolerant. Cetuximab–irinotecan or single-agent panitumumab in third line if KRAS wild type)

MANAGEMENT OF COLON CANCER (CONT'D)

Related Topics
Cancer Screening (p. 240)
Chemotherapy-Induced Diarrhea (p. 257)
Oral Mucositis (p. 256)
Hematochezia (p. 134)
Hereditary Cancers (p. 243)

MANAGEMENT OF RECTAL CANCER

HIGHLY RESECTABLE (stage I)—**transanal excision** only if T1, <30% circumference, <3 cm [<1.2 in.], margins >0.3 cm [>0.12 in.], mobile, within 8 cm [3.1 in.] of anal verge, no lymphovascular or perineural invasion, well or moderately differentiated tumor, and no evidence of lymphadenopathy on pretreatment imaging. Otherwise, **total mesorectal excision** via low anterior resection or abdominoperineal resection

RESECTABLE (stage II and some stage III with no high risk feature (not fixed, not low <5 cm [2 in.], not bulky)—**neoadjuvant radiation** (short course, 1 week) + **total mesorectal excision** + **adjuvant chemotherapy** based on pathologic stage: FOLFOX × 12 if pathologic node positive (i.e. node positive); capecitabine × 8 if pathologic node negative. The type and the number of cycles of adjuvant chemotherapy are, however, not well established. Local guideline may vary. Neoadjuvant chemoradiation is also an appropriate option for these patients

POSSIBLY RESECTABLE (locally advanced disease, particularly if tethered to rectum or low-lying tumor <5 cm [<2 in.] from anus)—**neoadjuvant chemoradiation** (long course, 5 weeks, 5040 cGy plus infusional 5-fluorouracil or capecitabine) + **total mesorectal excision** + **adjuvant chemotherapy** for 4 months. Capecitabine or FOLFOX may be considered depending on the extent of downstaging with neoadjuvant chemoradiation and the pathologic stage

METASTATIC (stage IV)—see management for stage IV colon cancer

NOTE: FOLFOX = 5-fluorouracil, leucovorin, and oxaliplatin; FOLFIRI = 5-fluorouracil, leucovorin, and irinotecan; 5-fluorouracil/LV = 5-fluorouracil and leucovorin

TREATMENT ISSUES

ESTIMATED BENEFITS OF ADJUVANT CHEMOTHERAPY FOR STAGE III COLORECTAL CANCER

RELATIVE RISK REDUCTION FROM ADJUVANT ONLINE

	Recurrence	Death
5-FU benefit		
Node –ve	20%	18%
Node +ve	43%	38%
FOLFOX benefit		
Node –ve	39%	24%
Node + ve	59%	48%

COLORECTAL CANCER SURVEILLANCE—for patients with stage II and III disease who would be candidate for salvage treatment if recurrence, surveillance includes medical visit with history, physical examination and CEA every 3–6 months × 2 years, then every 6 months for the next 3 years. CT chest/abd (+ CT pelvis for rectal cancer) yearly × 5 years. Colonoscopy at 1 year and 3 years after initial diagnostic colonoscopy, then every 5 years. Proctosigmoidoscopy every 6 months for 5 years if rectal cancer but radiation not given

TREATMENT ISSUES (CONT'D)

MODULATORS OF 5-FLUOROURACIL ACTIVITY—leucovorin (LV) promotes formation of a stable ternary complex with thymidylate synthetase, permitting prolonged inhibition of the enzyme by 5-fluorouracil

LIVER RESECTION CRITERIA

- **RESECTABLE DISEASE**—involvement of <70% of liver and <6 segments, no involvement of major vessels including SMA, SMV, hepatic vein, hepatic artery, portal vein, and no metastases elsewhere. An evaluation by a hepatobiliary surgeon should always be considered
- **OPERABLE CANDIDATE**—relatively young, no major comorbidities, performance status 0–1
- **PREDICTIVE FACTORS OF RECURRENCE POST-LIVER METASTASECTOMY**—tumor >5 cm [>2 in.], >1 liver lesion, lymph node involvement, relapse-free survival <1 year, CEA >200 μg/L within 1 month post-surgery

Carcinoid Tumors NEJM 1999 340:11

PATHOPHYSIOLOGY

CLASSIFICATION OF NEUROENDOCRINE TUMORS

- **HIGH GRADE**—poorly differentiated neuroendocrine carcinomas, small cell-like tumors
- **LOW GRADE**—carcinoid tumors, pancreatic islet tumors (VIPoma, glucagonoma, gastrinoma, insulinoma, somatostatinoma), paragangliomas, pheochromocytomas, medullary thyroid carcinomas

CLASSIFICATION BY LOCATION

- **FOREGUT CARCINOID**—lungs, bronchi, stomach
- **MIDGUT CARCINOID**—small intestine, appendix, proximal large bowel
- **HINDGUT CARCINOID**—distal colon, rectum, genitourinary tract

SPECIFIC DETAILS BY LOCATION

- **LUNGS AND BRONCHI**—derived from epithelial endocrine cells
  - **WELL-DIFFERENTIATED NEUROENDOCRINE TUMOR** (typical carcinoid, 67%)—more indolent. May secrete corticotrophin but rarely secretes serotonin; 90% 5-year survival
  - **WELL-DIFFERENTIATED NEUROENDOCRINE CARCINOMA** (atypical carcinoid, 33%)—may be aggressive with high chance of metastases; 40–60% 5-year survival

PATHOPHYSIOLOGY (CONT'D)

- **STOMACH**—derived from enterochromaffin-like cells
  - **TYPE 1: CHRONIC ATROPHIC GASTRITIS-TYPE-A-ASSOCIATED CARCINOID TUMOR** (75%)—indolent, usually multiple, not associated with carcinoid syndrome
  - **TYPE 2: CARCINOID TUMOR ASSOCIATED WITH ZOLLINGER-ELLISON SYNDROME OR MEN-1** (5–10%)—indolent, may be multiple, not associated with carcinoid syndrome
  - **TYPE 3: SPORADIC CARCINOID TUMOR** (15–25%)—may be aggressive with high chance of metastases. Contain a variety of endocrine cells. May be associated with atypical carcinoid syndrome
- **SMALL BOWEL**—derived from intraepithelial endocrine cells. Often multiple, usually in ileum. Associated with carcinoid syndrome in 5–7% of patients with liver metastasis (first-pass metabolism)
- **APPENDIX**—carcinoid tumors are the most common neoplasms in the appendix. Derived from subepithelial endocrine cells. Usually indolent
- **COLON**—derived from epithelial endocrine cells. Usually right sided, often presents at late stage

PATHOPHYSIOLOGY (CONT'D)

- **RECTUM**—derived from epithelial endocrine cells. Carcinoid syndrome rare

Related Topics
Wheezing (p. 1)
Chronic Diarrhea (p. 138)
MEN syndrome (p. 397)

FUNCTIONALITY—carcinoid tumors arise from neuroendocrine cells. Contain membrane-bound neurosecretory granules such as serotonin, histamine, dopamine, substance P, neurotensin, prostaglandins, kallikrein, ACTH, calcitonin, gastrin. Release of these vasoactive agents leads to episodic symptoms. However, about 50% of tumors are non-secretory and thus non-functional

SEROTONIN SYNTHESIS—5-hydroxytryptophan (with aromatic acid decarboxylase) → serotonin (with monoamine oxidase) → 5-hydroxyindoleacetic acid (5-HIAA) → excreted in urine

METASTASIS—liver and sometimes bones (osteoblastic)

CLINICAL FEATURES

GENERAL—the majority of patients are asymptomatic (10% of small intestine in the presence of liver metastases, <1% appendix, none in the rectum are associated with the carcinoid syndrome); 75–80% of patients with the carcinoid syndrome have small bowel carcinoids

LOCAL—obstruction (airway, bowel), pain (abdominal), bleeding

NEUROENDOCRINE SYNDROMES (30–40% of tumors active)—serotonin mainly (episodic purplish flushing, diarrhea, wheezing, hypotension and eventually right-sided valvular heart disease), fibrosing mesenteritis, Cushing's, acromegaly (rare). Attacks may be spontaneous or precipitated by stress, exercise, eating or alcohol use, palpation of the liver and anesthesia. Gastric and bronchial carcinoids are associated with atypical carcinoid syndromes (histamine). Somatostatinoma is associated with the triad of diabetes mellitus (insulin release impaired), cholelithiasis (reduced gallbladder contractility), and diarrhea/steatorrhea (pancreatic insufficiency)

NIACIN DEFICIENCY—pellagra as tryptophan directed to production of serotonin

METASTASIS—jaundice, liver failure, bone pain

CARCINOID HEART DISEASE—occurs in 1/2 of patients with carcinoid syndrome. Factors (e.g. serotonin) secreted by liver metastases

CLINICAL FEATURES (CONT'D)

into hepatic vein → plaque like, fibrous endocardial thickening involving the right side of the heart → tricuspid regurgitation most common. Tricuspid stenosis, pulmonary regurgitation, and pulmonary stenosis may also occur. Pulmonary carcinoids may produce left-sided valvular disease

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, serum chromogranin A, 24 h urine 5-HIAA (sens 73%, spc 100%)
- **IMAGING**—CT chest/abd/pelvis, somatostatin scintigraphy (sens 89%), MIBG scan (useful if somatostatin scan negative). Echocardiogram
- **BIOPSY**—ensure pathology includes Ki67 immunohistochemistry

SPECIAL

- **PANCREATIC NEUROENDOCRINE TUMOR WORKUP**—pancreatic polypeptide, α-hCG, chromogranin A, gastrin, somatostatin, serum VIP, glucagon, insulin and C-peptide levels
- **SERUM SEROTONIN**—when urinary 5-HIAA equivocal
- **EPINEPHRINE OR PENTAGASTRINE PROVOCATION TESTS**—if flushing and normal markers

MANAGEMENT

SYMPTOM CONTROL (AVOID PRECIPITATING FACTORS)

- **DIARRHEA**—*octreotide* 100–600 μg SC div 2–4 doses, *octreotide depot* 10–30 mg IM every 28 days, lanreotide, *loperamide* 4 mg × 1 dose, then 2 mg q4h PRN, maximum 16 mg/day, *atropine–diphenoxylate* 1–2 tabs q6–8 h, cyproheptadine, methysergide, *ondansetron* 8 mg PO TID. Gastric carcinoid can respond to a histamine blocker
- **HYPOTENSION**—pure α-adrenergic medications such as methoxamine and angiotensin. Corticosteroids may be useful for prophylaxis. Strictly avoid β-adrenergic agonists such as epinephrine and dopamine as they may aggravate hypotension
- **FLUSHING**—octreotide, *prochlorperazine* 10 mg PO QID (foregut), *phenoxybenzamine* 10–20 mg PO BID, *prednisone* 20–40 mg PO daily (foregut)
- **BRONCHOSPASM**—salbutamol 2 puffs INH q4h PRN, ipratropium, theophylline

MANAGEMENT (CONT'D)

- **CARCINOID HEART DISEASE**—medical management of heart failure, valvular replacement may be considered but patients are usually high-risk surgical candidates

LOCALIZED DISEASE—resection

ADVANCED/METASTATIC DISEASE

- **PALLIATIVE RESECTION**—for debulking, prevention of mesenteric fibrosis by mid-gut carcinoids, and treatment of obstruction and extraintestinal primary tumors such as bronchial and ovarian carcinoids that rarely cause carcinoid syndrome without hepatic metastasis
- **CHEMOTHERAPY**—limited activity, streptozocin/5-fluorouracil or doxorubicin, interferon α (now rarely used). Consider temozolomide, cisplatin, and etoposide for patients with poorly differentiated tumors
- **TARGET RADIOTHERAPY WITH RADIOLABELED SOMATOSTATIN ANALOGUES**—difficult to access as only few institutions offer this therapy
- **HEPATIC METASTASES**—resection, radiofrequency ablation and cryoablation, hepatic artery embolization

TREATMENT ISSUES

SOMATOSTATIN ANALOGUES—octreotide is a long-acting somatostatin analogue that binds to somatostatin receptor 2 and to a certain extent

TREATMENT ISSUES (CONT'D)

receptors 3 and 5 and inhibits secretion of various hormones

- **INDICATIONS**—symptomatic with hormone-induced syndromes. Can be used in asymptomatic patients to delay progression for midgut tumors, and perioperatively to prevent carcinoid crisis. Controversial indications include post-surgery, post-embolization or radiofrequency ablation, and post-adjuvant treatment with no evidence of disease
- **DOSING**—give 50 μg as test dose (may cause gastric atony and skin toxicity), then 100–150 μg SC BID–TID. May double dose every 3–4 days until symptom free. Once on a stable dose, may switch to long-acting formulation (200–600 μg/day → 20 mg/month or 750–1500 μg/day → 30 mg/month). Continue life long
- **ADVERSE EFFECTS**—nausea, gastric atony, abdominal cramps, diarrhea/constipation, gallstones, impaired glucose tolerance, hypothyroidism, dyspnea, arrhythmia, HTN, fatigue, headache, dizziness, fever, flu-like symptoms

FOLLOW-UP—clinical assessment along with chromogranin A and 24 h urine 5-HIAA every 3–6 months, routine imaging every 6–12 months

Gastrointestinal Stromal Tumor

PATHOPHYSIOLOGY

HISTOLOGY—spindle cell or epithelioid tumor that may be derived from interstitial cells of Cajal (pacemaker cells involved in peristalsis)

LOCATIONS—stomach (50%), small intestine (25%), colon (10%), esophagus, rectum, mesentery, and retroperitoneum

MOLECULAR BIOLOGY—characteristic c-kit/CD117 (90%) and/or PDGFRa mutation, CD34+ (66%)

NATURAL HISTORY—clinical behavior of GIST is variable and the risk of recurrence and metastases depends on various adverse prognostic factors. Metastases most commonly involve liver, rarely regional lymph nodes and almost never lungs

CLINICAL FEATURES

LOCOREGIONAL—GI bleed, abdominal mass, abdominal pain

METASTATIC—RUQ pain, jaundice

TREATMENT ISSUES (CONT'D)

CONSTITUTIONAL—weight loss, anorexia, fatigue, hypoglycemia from secretion of IGFII (rare)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin
- **IMAGING**—CT abd/pelvis ± MRI, US abd, chest imaging, PET/CT in selected patients
- **BIOPSY**—endoscopy, laparotomy. Consider KIT and PDGRA mutational testing for KIT-negative tumors

PROGNOSTIC ISSUES

ADVERSE PROGNOSTIC FACTORS—size, mitotic rate, tumor site (small intestine worse), incomplete resection (<35% vs. 50–65% 5-year survival)

PROGNOSTIC ISSUES (CONT'D)

PREDICTIVE FACTORS—exon 11 KIT mutation is predictive of response to imatinib compared to exon 9 KIT mutation or wild type

MANAGEMENT

RESECTABLE DISEASE—segmental resection without regional lymphadenectomy. Adjuvant *imatinib* 400 mg PO daily is recommended for 36 months for patients with high-risk GIST

UNRESECTABLE, RECURRENT, OR METASTATIC DISEASE—*imatinib* 400 mg/day (until disease progression) is recommended, except for exon 9 mutation in which *imatinib*

MANAGEMENT (CONT'D)

800 mg/day is appropriate. For patients with non-metastatic but unresectable disease, consider neoadjuvant imatinib followed by resection if possible. For patients with potentially resectable metastatic GIST, surgery should be offered to those with stable disease, responding to tyrosine kinase inhibitor therapy, or with focal progression only. Hepatic chemoembolization could be considered in isolated unresectable liver metastases. If progression on imatinib, increase dose to 800 mg/day. With further disease progression, consider second line sunitinib and third line regorafenib

Anal Cancer

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY (WHO)

- **ANAL CANAL**
  - **SQUAMOUS CELL CARCINOMA** (**75**%)—large cell keratinizing (distal to the dentate line) or non-keratinizing (above the dentate line)
  - **ADENOCARCINOMA** (**20**%)—rectal type, of anal glands, within anorectal fistula
  - **SMALL CELL CARCINOMA**
  - **UNDIFFERENTIATED**
- **ANAL MARGIN (PERIANAL SKIN)**
  - **SQUAMOUS CELL CARCINOMA**
  - **GIANT CONDYLOMA**
  - **BASAL CELL CARCINOMA**
  - **OTHERS**—Bowen's disease, Paget disease

RISK FACTORS

- **PERSONAL**—sexual activity (HPV, number of sexual partners, receptive anal intercourse, history of STD, genital warts)
- **ENVIRONMENTAL**—smoking
- **DISEASES**—HIV and other causes of chronic immunosuppression (e.g. solid organ transplantation).

LYMPHATIC DRAINAGE

- **TUMORS ORIGINATING ABOVE THE DENTATE LINE**—drain to the perirectal and paravertebral LN
- **TUMORS ORIGINATING BELOW THE DENTATE LINE**—drain to the inguinal and femoral LN

CLINICAL FEATURES

LOCOREGIONAL—rectal bleeding (45%), anal pain, and sensation of rectal mass (30%). Squamous cell carcinoma may be associated with a history of anorectal condyloma (50%), while tumor of perianal skin can be associated with pruritus ani

METASTATIC—RUQ pain, dyspnea

CONSTITUTIONAL—weight loss, anorexia, fatigue

STAGING

TNM STAGING (7TH EDITION)

T stage

- **T1** ≤ 2 cm
- **T2** > 2 cm but ≤5 cm
- **T3** > 5 cm
- **T4** = invades adjacent organ(s) (involvement of sphincter muscle(s) alone is not classified as T4)

N stage

- **N1** = perirectal LN
- **N2** = unilateral internal iliac LN and/or inguinal LN
- **N3** = perirectal and inguinal LN and/or bilateral internal iliac and/or inguinal lymph nodes

M stage

- **M1** = distant metastasis

STAGE GROUPINGS

Stage	TNM @ = any	Freq	5-year survival
I	T1N0M0	10%	85%
II	T2-T3N0M0	55%	75%
IIIA	T1–3N1M0, T4N0M0	27%	54%
IIIB	T4N1M0, T@N2-3M0		
IV	T@N@M1	6%	17%

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, HIV testing
- **IMAGING**—CXR, CT chest, CT, or MRI abd/pelvis ± PET/CT
- **BIOPSY**—mass biopsy

MANAGEMENT

SQUAMOUS CELL CANCER OF THE ANAL CANAL—chemoradiation (5-fluorouracil–mitomycin). If evidence of progression after treatment, consider salvage abdominoperineal resection. For metastatic disease, consider palliative chemotherapy (5-fluorouracil–cisplatin), regional therapy for isolated hepatic metastases

MANAGEMENT (CONT'D)

PRIMARY ADENOCARCINOMA OF THE ANAL CANAL—managed like rectal cancer

CANCER OF THE PERIANAL SKIN—treated like skin counterpart

Cancer of the Exocrine Pancreas

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY

- **ADENOCARCINOMA** (85–90%)—male predominance, 60% arising from head of pancreas, metastasizes widely
- **DUCTAL CARCINOMAS**
- **ADENOSQUAMOUS CARCINOMA**—rare variant of ductal adenocarcinoma, history of prior chemotherapy or radiotherapy, relatively poor prognosis
- **COLLOID CARCINOMA** (1–2%)—composed of pools of mucous that contains clusters of malignant duct cells
- **ACINAR CELL CARCINOMA** (1%)—lipase release, equal distribution throughout pancreas
- **MUCINOUS CYSTIC NEOPLASMS** (1%)—cystic, significant malignant potential, strong female predominance, 70–90% in pancreatic body/tail
- **SEROUS CYSTOADENOMAS**—cystic, benign
- **SEROUS CYSTADENOCARCINOMA**—cystic, malignant behavior
- **SOLID AND PSEUDOPAPILLARY CYSTIC TUMORS**—young female (childbearing) predominance, local invasion into adjacent structures common but metastases rare, frequent intracystic hemorrhage
- **INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM**—male predominance, benign lesion with high potential for malignant change
- **PANCREATOBLASTOMA**—rare (0.5%); first and second decades of life, prognosis better than for infiltrating ductal carcinoma
- **MISCELLANEOUS CANCERS**—liposarcomas, leiomyosarcomas, fibrosarcomas, and lymphomas
- **OTHER LESS COMMON VARIANTS**—pleomorphic, sarcomatoid, and giant cell carcinomas

RISK FACTORS

- **PERSONAL**—Ashkenazi Jewish origin, low socioeconomic status, habitation of industrialized societies, obesity, and low physical activity

PATHOPHYSIOLOGY (CONT'D)

- **FAMILY HISTORY**—HNPCC, FAP, BRCA1/2 gene, hereditary pancreatitis, ataxia telangiectasia, Peutz–Jeghers syndrome, familial atypical multiple mole melanoma syndrome (FAMMM), Li–Fraumeni syndrome
- **ENVIRONMENTAL**—smoking
- **DISEASES**—chronic pancreatitis, diabetes (may be a manifestation of early disease rather than a true risk factor), pernicious anemia, partial gastrectomy

CLINICAL FEATURES

LOCOREGIONAL—abdominal pain (80%), jaundice (50%), pruritus, altered bowel habits (steatorrhea, pale stools), glucose intolerance

METASTATIC—RUQ pain, dyspnea

CONSTITUTIONAL—weight loss, anorexia, fatigue

OTHERS—Trousseau's syndrome, polymyositis, dermatomyositis, panniculitic arthritis–eosinophilia syndrome, depression

STAGING

TNM STAGING (7TH EDITION)

T stage

- **T1** ≤ 2 cm, limited to pancreas
- **T2** > 2 cm, limited to pancreas
- **T3** = extends beyond pancreas, but not involving celiac axis or superior mesenteric artery
- **T4** = invades celiac axis or superior mesenteric artery

N stage (portal, peripancreatic, periaortic, celiac axis LN)

- **N1** = regional LN

M stage (liver, lungs, bone, pleura, adrenal)

- **M1** = distant metastasis

STAGING (CONT'D)

STAGE GROUPINGS

Stage	TNM @ = any	Freq.	Median survival (months)
IA	T1N0M0	10%	17
IB	T2N0M0		
IIA	T3N0M0		
IIB	T1–3N1M0	20–30%	8–9
III	T4N@M0		
IV	T@N@M1	50–60%	4–6

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, lipase, CA 19–9, CEA
- **IMAGING**—CXR, CT abd (allows for establishment of resectability criteria, >90% accurate in the staging), US abd, endoscopic US (EUS), MRCP
- **BIOPSY**—percutaneous needle biopsy (only if unresectable disease), endoscopic US-guided biopsy, ERCP (also useful for treatment of biliary obstruction), laparoscopy, laparotomy

DIAGNOSTIC ISSUES

CT FINDINGS FOR PANCREATIC CANCER—mass (identified in 96% of cases), dilatation of the bile and pancreatic ducts (double-duct sign) suggests a pancreatic head lesion, dilatation of the pancreatic duct proximal to the tumor, atrophy of the pancreas distal to a tumor

MANAGEMENT

RESECTABLE (T1-3N0–1, 10–20%)—**Whipple's procedure** plus either **adjuvant chemotherapy** (gemcitabine or 5-fluorouracil) or **adjuvant chemoradiation** (5-fluorouracil) ± gemcitabine in selected patients)

MANAGEMENT (CONT'D)

NON-RESECTABLE (locally advanced and metastatic disease)

- **PALLIATIVE CHEMOTHERAPY**—if good performance status, consider FOLFIRINOX (5-fluorouracil –leucovorin–irinotecan-oxaliplatin). If borderline performance status, consider gemcitabine-nab-paclitaxel or gemcitabine ± erlotinib. Other potential options include gemcitabine-capecitabine, gemcitabine-cisplatin, FOLFOX, XELOX, single agent gemcitabine, single agent capecitabine, or infusional 5-flurouracil
- **CHEMORADIATION** (5-fluorouracil)—in selected patients with limited advanced unresectable cancer
- **PAIN CONTROL**—opioids, percutaneous celiac ganglion ablation
- **ANOREXIA-CACHEXIA**—nutrition supplements, steroids
- **PALLIATIVE RADIATION**—controversial with no clear benefit
- **PALLIATIVE PROCEDURES**—if biliary obstruction, consider ERCP stent placement or percutaneous transhepatic cholangiography with drainage

TREATMENT ISSUES

RESECTABLE DISEASE CRITERIA

1. No liver, peritoneal, or other metastases
2. No involvement of celiac axis, superior mesenteric artery, and hepatic artery
3. No encasement of portal vein and superior mesenteric vein (*adherence* of the tumor to a segment of these veins *may* allow resection with venous reconstruction)

If in doubt, patients should be evaluated by a hepatobiliary surgeon

Related Topics
Cachexia (p. 449)
Cancer Pain (p. 442)
Jaundice (p. 155)

Hepatocellular Carcinoma

DIFFERENTIAL DIAGNOSIS OF FOCAL LIVER LESION (BY ULTRASOUND)

SOLID LESION

- **HYPOECHOIC**—**malignant** (hepatocellular carcinoma, metastasis), **benign** (focal nodular hyperplasia, hepatic adenoma, hamartoma)
- **HYPERECHOIC**—hemangioma, calcification, focal fat

CYSTIC LESION

- **SIMPLE**—benign
- **COMPLEX**—bleeding, infections, *Echinococcus*

PATHOPHYSIOLOGY

RISK FACTORS—any causes of cirrhosis, particularly HBV, HCV, alcohol, and hemochromatosis. Note that HBV may cause hepatocellular carcinoma without cirrhosis as the virus can integrate into host genome. Environmental toxins include aflatoxin, the bluegreen algal toxin Microcystin, and betelnut chewing

CLINICAL FEATURES

LOCOREGIONAL—upper abdominal pain, early satiety, obstructive jaundice, intra-abdominal bleeding due to tumor rupture, decompensation of liver disease (ascites, encephalopathy, jaundice, and variceal bleeding)

METASTATIC—bone pain, dyspnea

CONSTITUTIONAL—weight loss, fever due to central tumor necrosis

PARANEOPLASTIC SYNDROME—hypoglycemia, erythrocytosis, hypercalcemia, watery diarrhea, cutaneous features

STAGING FOR HEPATOCELLULAR CARCINOMA OR INTRAHEPATIC BILE DUCT CANCER

TNM STAGING (7TH EDITION)

T stage

- **T1** = solitary tumor without vascular invasion
- **T2** = solitary tumor with vascular invasion or multiple tumors ≤5 cm
- **T3** = multiple tumors >5 cm or tumor that involves major branch of portal or hepatic vein
- **T4** = invades adjacent structures other than gallbladder or with perforation of the visceral peritoneum

N stage (along portal vein, hepatic artery, inferior vena cava, hepatoduodenal ligament)

- **N1** = regional LN

DIFFERENTIAL DIAGNOSIS OF FOCAL LIVER LESION (BY ULTRASOUND) (CONT'D)

M stage

- **M1** = distant metastasis

STAGE GROUPINGS

Stage	TNM @ = any	5-year survival
I	T1N0M0	55%
II	T2N0M0	37%
IIIA	T3aN0M0	16%
IIIB	T3bN0M0	
IIIC	T4N0M0	
IVA	T@N1M0	<5%
IVB	T@N@M1	

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, PTT, albumin, AFP
- **IMAGING**—CXR, CT abd (biphasic or triphasic), US abd, MRI abd, liver/spleen scan (if suspect FNH)

SPECIAL

- **BIOPSY**—liver biopsy only if non-specific imaging and meeting AASLD clinical criteria (>1 cm, atypical vascular pattern on multiple imaging modalities including multiphase CT or MR) or if biopsy would have an impact on management options; if imaging definitive for HCC, biopsy not required and increases risk of seeding needle track

DIAGNOSTIC ISSUES

CT SCAN—characteristic features for hemangioma, FNH (central scar)

LIVER SPLEEN SCAN—useful for distinguishing focal nodular hyperplasia and hepatoma

GALLIUM SCAN—useful for identifying hepatoma and abscesses (increased blood flow)

APPROACH TO HEPATOMA—start with US abd, followed by CT/nuclear scans to rule out other causes

- **LOW CLINICAL SUSPICION**—consider percutaneous biopsy
- **HIGH CLINICAL SUSPICION** (known cirrhosis)—patient should be referred to hepatobiliary surgeon for resection. Biopsy is not required

MANAGEMENT

EARLY STAGE (1 lesion or 3 lesions ≤3 cm, Child–Pugh A-B, and ECOG 0)—if only 1 lesion <2 cm or CIS, bilirubin not significantly elevated and no portal hypertension, proceed to resection. If unresectable disease, consider liver transplant if no comorbidity plus either 1 lesion ≤5 cm or up to 3 lesions ≤3 cm (Milan Criteria). Consider locoregional therapies such as radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE) ± drug eluting beads, and/or transarterial radioembolization (TARE) with Yttrium-90 microspheres as either bridge therapy while waiting for transplant, downstaging therapy so tumor is small enough for transplant or if patient is not transplant candidate

INTERMEDIATE STAGE (multinodular disease, Child–Pugh A-B, and ECOG 0)—chemoembolization. Median survival 6–16 months

ADVANCED STAGE (portal invasion, N1, M1, Child– Pugh A–B, or ECOG 1–2)—for patients with Child–Pugh A disease, consider sorafenib. Chemoembolization may also represent an option for some patients. Median survival 6–16 months

TERMINAL STAGE (Child–Pugh C or ECOG >2)—supportive care only. Median survival <3 months

Barcelona Clinic Treatment Algorithm

TREATMENT ISSUES

CRITERIA FOR RESECTABLE DISEASE—well-compensated cirrhosis, single lobe involvement, no vascular invasion, N0, M0

ABLATION—include thermal (radiofrequency), chemical (percutaneous ethanol or acetic acid), cyro and microwave ablation. Criteria for ablation include 1 lesion ≤5 cm or 3 lesions ≤3 cm, accessible location to percutaneous/laparoscopic/open approaches. Tumors ≤3 cm may be curable with ablation alone

TREATMENT ISSUES (CONT'D)

ARTERIAL DIRECTED THERAPIES—include TACE, TACE with drug-eluting beads, TARE, and transarterial bland embolization (TAE). Useful for larger volume disease or tumors in inaccessible location. Relative contraindications include bilirubin >3 mg/dL, portal vein thrombosis, and Child Pugh C. Adverse effects include decompensated liver failure, cholecystits, and non-target embolization. No proven survival benefit but can shrink tumor

FOLLOW-UP OF RESECTABLE DISEASE—AFP and CT abd every 3-6 months for 2 years, then every 6-12 months

SPECIFIC ENTITIES

HEMANGIOMA—prevalence 5%. May gradually increase in size due to vascular expansion. Usually asymptomatic and no treatment required

FOCAL NODULAR HYPERPLASIA (FNH)—prevalence 0.5%. Hyperplasia of liver cells in response to hyperperfusion from an anomalous artery. Rarely exceeds 10 cm. Usually asymptomatic

HEPATIC ADENOMA—mainly in young woman on oral contraceptive pills. May cause abdominal pain. Potential for malignant transformation. Treat initially by withdrawal of oral contraceptives and follow lesions by ultrasound. If fail to regress, consider resection

Related Topics
Hepatitis B (p. 145)
Hepatitis C (p. 147)
Hepatic Failure (p. 144)
Chronic Liver Disease (p. 149)

Renal Cancer

NEJM 2005 335:12
Cancer 2006 107:10

DIFFERENTIAL DIAGNOSIS OF SOLID RENAL MASS

RENAL MALIGNANCIES

ANGIOMYOLIPOMA—distinctive fat density on CT. Association with tuberous sclerosis

ONCOCYTOMA—a homogeneous, well-circumscribed solid mass with a central scar

XANTHOGRANULOMATOUS PYELONEPHRITIS —variant of chronic pyelonephritis

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY

- **RENAL CELL CARCINOMA** (80–85%)
- **CLEAR CELL** (75–85%)—proximal tubule
  - **PAPILLARY/CHROMOPHILIC** (12–14%)—proximal tubule
  - **CHROMOPHOBIC** (4–6%)—intercalated cell of cortical collecting duct
  - **ONCOCYTIC** (2–4%)—intercalated cell of cortical collecting duct

PATHOPHYSIOLOGY (CONT'D)

- **COLLECTING DUCT** (1%)—medullary collecting duct
- **TRANSITIONAL CELL CARCINOMA** (15–20%)—usually arises from the renal pelvis
- **LYMPHOMA**
- **SARCOMA**
- **RENINOMA**—usually arises from the juxtaglomerular cells. Mostly benign. May secrete renin
- **HEMANGIOPERICYTOMAS**—usually secrete renin. May be malignant
- **WILM'S TUMOR**—nephroblastomas. In children mostly

RISK FACTORS

- **PERSONAL**—age, obesity
- **ENVIRONMENTAL**—smoking (2x), phenacetin
- **FAMILY HISTORY**—affected relatives
- **DISEASES**—von Hippel–Lindau syndrome, hereditary type 2 papillary renal cell carcinoma, Birt–Hogg–Dube syndrome, autosomal dominant polycystic kidney disease

CLINICAL FEATURES

LOCOREGIONAL—classic triad of flank pain, hematuria, and abdominal mass. Other symptoms include varicocele (left > right due to obstruction of testicular vein), ascites, and leg swelling (if inferior vena cava involvement). Two-thirds of renal tumors are found incidentally

METASTATIC—dyspnea, bone pain, jaundice

CONSTITUTIONAL—fever, weight loss, anorexia, fatigue

PARANEOPLASTIC SYNDROMES—hypertension (40%, due to renin secretion), hypercalcemia (5%), polycythemia (5%, due to EPO secretion), anemia, thrombocytosis, AA amyloidosis, hepatic dysfunction (Stauffer's syndrome, without liver metastases)

STAGING

TNM STAGING (7TH EDITION)

T stage

- **T1** = <7 cm (T1a = <4 cm, T1b = 4–7 cm)
- **T2** = >7 cm (T2a = 7-10 cm, T2b >10 cm)
- **T3** = extends into surrounding structures but not Gerota fascia (T3a = extends into renal veins or invades adrenal gland or perinephric tissues, T3b = extends into vena cava below diaphragm, T3c = extends into vena cava above diaphragm)
- **T4** = invades beyond Gerota fascia

N stage

- **N1** = regional lymph node(s)

M stage (lungs, liver, bones, brain)

- **M1** = distant metastasis

STAGING (CONT'D)

STAGE GROUPINGS

Stage	TNM @ = any	5-year survival
I	T1N0M0	96%
II	T2N0M0	82%
III	T1-3N1M0, T3N0M0	64%
IV	T4N@M0, T@N@M1	23%

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, urinalysis (hematuria, proteinuria)
- **URINE CYTOLOGY**
- **IMAGING**—CXR, US abd, CT abd/pelvis (most useful), IVP, bone scan (if suspicious), MRI head (if suspicious)
- **NEPHRECTOMY**—biopsy is usually not required prior to surgery for solitary renal mass because of its low specificity and potential for seeding. Nephrectomy is both diagnostic and therapeutic

DIAGNOSTIC AND PROGNOSTIC ISSUES

ADVERSE PROGNOSTIC FACTORS— > 10 cm, stage III–IV, Fuhrman's grade 3–4 (based on nuclear size and shape, and nucleolar appearance, a score of 1–4 is given)

MSK PROGNOSTIC SCORE FOR METASTATIC RENAL CELL CARCINOMA—Karnofsky performance status <80%, LDH >1.5× upper normal limit, calcium >2.5 mmol/L [>10 mg/dL], hemoglobin < lower normal limit, absence of nephrectomy

Factors	Risk group	Freq.	1-year survival	3-year survival
0	Good	25%	71%	31%
1–2	Inter.	53%	42%	7%
3–5	Poor	22%	12%	0%

JCO 1999 17:8

MANAGEMENT

STAGE I—partial or radical nephrectomy ± regional node dissection

STAGE II—radical nephrectomy ± regional node dissection

STAGE III—radical nephrectomy ± regional node dissection ± renal vein or vena cava evacuation

MANAGEMENT (CONT'D)

STAGE IV

- **PALLIATIVE RESECTION**—nephrectomy (particularly if primary is symptomatic), systemic therapy intended, limited metastatic disease, good performance status, and good surgical candidate; resection of solitary metastasis may also be considered
- **PALLIATIVE TARGETED THERAPY FOR CLEAR CELL HISTOLOGY**
  - **FIRST LINE**—for good- or intermediate-risk disease, consider pazopanib, sunitinib or interferon plus bevacizumab. For poor-risk disease (MSK score ≥3), consider temsirolimus
  - **SECOND LINE**—everolimus, axitinib, sorafenib should be considered for cytokine refractory disease
- **PALLIATIVE RADIATION**—control of bleeding, pain or bone metastases
- **PALLIATIVE IMMUNOTHERAPY**—recombinant IL-2 or INFα, response rate 15–20%

SPECIFIC ENTITIES

VON HIPPEL–LINDAU DISEASE—a familial cancer syndrome due to mutation of the VHL gene. Disease spectrum includes renal cell carcinomas (clear cell type, 40%) and cysts, pancreatic carcinomas and cysts, pheochromocytomas, hemangioblastomas of the cerebellum and spinal cord, and retinal hemangiomas. HIF1α is hydroxylated in normoxic conditions, which is then ubiquitinated by VHL protein complex and destroyed. Accumulation of HIF1α happens with hypoxic conditions or mutated VHL protein, which then heterodimerizes with HIF1β and activates transcription of various genes such as VEGF. Development of targeted therapy for renal cell carcinoma was facilitated by our understanding of the VHL–HIF1α–VEGF pathway

Bladder Cancer

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY

- **TRANSITIONAL CELL** (90%)
- **SQUAMOUS** (8%)
- **ADENOCARCINOMA** (2%)
- **RHABDOMYOSARCOMA**
- **LYMPHOMA**
- **CARCINOID**

NATURAL HISTORY OF SUPERFICIAL TUMORS—low-grade superficial tumors have high recurrence rate (80%) and low risk of becoming invasive (10%). High-grade superficial tumors are frequently associated with carcinoma in situ, which is usually multifocal and has a high chance of becoming invasive (80% within 10 years)

RISK FACTORS

- **PERSONAL**—age
- **ENVIRONMENTAL**—smoking (4×), occupation (dye, rubber, textiles, leather, and petroleum industries with exposure to aniline, arylamines such as benzidine and 2-naphthylamine and amides), drugs (cyclophosphamide), pelvic radiation
- **FAMILY HISTORY**—affected relatives
- **DISEASES** (usually squamous cell carcinoma)—schistosomiasis, chronic bladder infection, Balkan endemic nephropathy

CLINICAL FEATURES

LOCOREGIONAL—painless intermittent hematuria (80%), bladder irritability (25%, hesitancy, urgency, frequency, and dysuria), abdominal mass, suprapubic or flank pain, lymphedema

METASTATIC—dyspnea, bone pain, jaundice

CONSTITUTIONAL—weight loss, anorexia, fatigue

PARANEOPLASTIC—hypercalcemia, systemic fibrinolysis, neuromuscular syndromes

STAGING

TNM STAGING (7TH EDITION)

T stage

- **Ta** = non-invasive papillary carcinoma
- **Tis** = carcinoma in situ (CIS), flat tumor
- **T1** = invades subepithelial connective tissue
- **T2** = invades muscularis propria (T2a = invades inner half superficial muscle, T2b = invades outer half deep muscle)
- **T3** = invades perivesical tissue (T3a = microscopic, T3b = macroscopic)
- **T4** = invades surrounding tissue (T4a = prostate, uterus, vagina, T4b = pelvic wall, abdominal wall)

STAGING (CONT'D)

N stage
- **N1** = single regional LN in the true pelvis (hypogastric, obturator, external iliac, or presacral)
- **N2** = multiple regional LN in the true pelvis
- **N3** = metastasis to the common iliac lymph nodes

M stage (bone, liver, lungs)
- **M1** = distant metastasis

STAGE GROUPINGS

Stage	TNM @ = any	5-year survival
0a	TaN0M0	>90%
0is	TisN0M0	
I	T1N0M0	85%
II	T2a-bN0M0	60%
III	T3a-bN0M0, T4aN0M0	35%
IV	T4bN0M0, T@N1-3M0, T@N@M1	15%

INVESTIGATIONS

BASIC
- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin
- **IMAGING**—IVP or triphasic CT abd/pelvis
- **URINE CYTOLOGY**—sens 70%
- **CYSTOSCOPY WITH BIOPSY**

PROGNOSTIC ISSUES

RISK FACTORS FOR RECURRENCE OF SUPERFICIAL BLADDER TUMOR POST-RESECTION—previous recurrence, large size, high grade, advanced stage (T1 > Tis > Ta) multiple tumors, diffuse CIS

ADVERSE PROGNOSTIC FACTORS—squamous cell carcinoma or adenocarcinoma, invasion of muscle, lymphatics, or perivesical fat

MANAGEMENT

SUPERFICIAL
- **STAGE 0A, 0IS, I**—**transurethral resection** (TUR) ± fulguration ± **intravesicular therapy** (BCG × 6 [bacillus Calmette–Guerin], mitomycin C, thiotepa, doxorubicin, epirubicin, Epodyl) ± intravesicular interferon. **Radical cystectomy** may be done if multifocal CIS

INVASIVE
- **STAGE II, STAGE III**—**radical cystectomy ± pelvic lymph node dissection** or **curative radiation**, **(neo)adjuvant chemotherapy** (gemcitabine–cisplatin [GC], methotrexate–vinblastine–doxorubicin–cisplatin [MVAC] or dose dense MVAC, cisplatin–methotrexate–vinblastine [CMV])
- **STAGE IV**—palliative chemotherapy (GC, MVAC, dose dense MVAC, CMV)

Prostate Cancer

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY
- **ADENOCARCINOMA** (>95%)
- **PROSTATE INTRAEPITHELIAL NEOPLASM** (PIN)
- **TRANSITIONAL CELL CARCINOMA**
- **SMALL CELL CARCINOMA**
- **SQUAMOUS CELL CARCINOMA**
- **SARCOMA**

GLEASON SCORE—assigned by a pathologist based on the aggressiveness of the predominate population (1–5) plus second most common population (1–5) with a total of between 2 and 10

RISK FACTORS
- **PERSONAL**—male, age, race (black > Caucasian > Asian)
- **FAMILY HISTORY**—affected relatives (2–5×)
- **ENVIRONMENTAL**—total and saturated fat intake

CLINICAL FEATURES

LOCOREGIONAL—mostly asymptomatic with diagnosis made by rise in PSA or incidentally through TURP for BPH. Potential symptoms include urinary obstruction, urinary frequency, nocturia, hesitancy, slow stream, urge incontinence

METASTATIC—bony pain, cord compression. Hypercalcemia and fractures are not very common as the metastatic lesions tend to be osteoblastic instead of lytic

CONSTITUTIONAL—weight loss, anorexia, fatigue

PARANEOPLASTIC—systemic fibrinolysis, neuromuscular syndromes

INTERNATIONAL PROSTATE SYMPTOM SCORE (IPSS)
- **SCORING**—symptoms of incomplete emptying, urinary frequency, intermittency, urgency, weak stream, straining and nocturia over the last month.

CLINICAL FEATURES (CONT'D)

Each symptom assigned a score from 0 to 5, with a total score ranging between 0 and 35

- **INTERPRETATION**—mild = 0–7, moderate = 8–19, severe = 20–35

STAGING

TNM STAGING (7TH EDITION)

T stage

- **T1** = clinically inapparent tumor (**T1a** = incidental finding by TURP in <5% of tissue, **T1b** = incidental finding by TURP in >5% of tissue, **T1c** = incidental finding by needle biopsy due to ↑ PSA)
- **T2** = confined within prostate (**T2a** = invades less than or equal to half of one lobe, **T2b** = invades more than half of one lobe, **T2c** = invades both lobes)
- **T3** = extends through the prostate capsule (**T3a** = extracapsular extension, **T3b** = invades seminal vesicle(s))
- **T4** = fixed or invades bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

N stage (obturator, hypogastric → iliac)

- **N1** = regional LN

M stage (bone, liver. Biologically heterogeneous with variable course)

- **M1** = distant metastasis

STAGE GROUPINGS

Stage	TNM
I	T1a-2aN0M0, PSA <10, Gleason ≤6
	T1a-2aN0M0, PSA X, Gleason ≤6
IIa	T1a-1cN0M0, PSA <20, Gleason 7
	T1a-2aN0M0 PSA 10 to <20, Gleason ≤6
	T2aN0M0, PSA <20, Gleason ≤7
	T2bN0M0, PSA <20, Gleason ≤7
	T2bN0M0, PSA X, Gleason X
IIB	T2cN0M0, Any PSA, Any Gleason
	T1-2N0M0, PSA ≥20, Any Gleason
	T1-2N0M0, Any PSA, Gleason ≥8
III	T3a-bN0M0, Any PSA, Any Gleason
IV	T4N0M0, Any PSA, Any Gleason
	T@N1M0, Any PSA, Any Gleason
	T@N@M1, Any PSA, Any Gleason

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, PSA, testosterone
- **IMAGING**—CXR, CT or MRI abd/pelvis (if high-risk disease), bone scan (if high-risk disease)
- **BIOPSY**—US-guided transrectal biopsy (6–12 core needles)

Related Topics
Cancer Screening (p. 240)
Tumor Markers (p. 239)

DIAGNOSTIC AND PROGNOSTIC ISSUES

PROSTATE-SPECIFIC ANTIGEN—a serine protease that liquifies semen physiologically. Elevated in prostate cancer, prostatitis, BPH, endoscopy, prostate surgery, prostate biopsy (remains elevated for 6–8 weeks), and with increasing age (normal PSA by age: age 40–50 < 2.5 ng/mL, age 50–60 < 3.5 ng/mL, age 60–70 < 4.5 ng/mL, age 70–80 < 6.5 ng/mL). May be used for screening, diagnosis, prognostication, and following treatment response

- **FREE PSA**—proportion of PSA unbound to antichymotrypsin or α2 macroglobulin. A decreased ratio of free to total PSA is associated with higher chance of prostate cancer
- **PSA DENSITY**—PSA/prostate volume and may be associated with increased PPV and NPV
- **SCREENING**—PSA >4 ng/mL is considered abnormal, spc 32%. With the addition of DRE, spc 48%. A PSA increase of 20%/year also should warrant a biopsy. So far, PSA screening has not been proven to reduce mortality from prostate cancer. Discuss potential risks/benefits with men >50 years, high risk (family history, ethnicity)
- **BIOCHEMICAL RELAPSE**—for patients with previous prostatectomy, PSA relapse is indicated by any detectable value, particularly if >1 ng/mL. For patients with previous external beam radiation or brachytherapy, PSA relapse is indicated by PSA >2 ng/mL from nadir

ADVERSE PROGNOSTIC FACTORS—pretreatment PSA, Gleason score, stage

RISK CATEGORIES FOR LOCALIZED DISEASE

Risk category	PSA (ng/mL)	Gleason score	Stage
Low (highly curable)	<10	2–6	≤T2a
Intermediate (curable)[a]	10–20	7	T2b-c
High (rarely curable)	>20	8–10	≥T3a

[a]If more than one risk factors present, consider shifting to high risk group

MANAGEMENT

LOCALIZED DISEASE (T1-3N0M0)

- **LOW RISK**—consider active surveillance if significant comorbidities or <10-year life expectancy. Patients on active surveillance should have PSA testing every 6 months and prostate biopsy yearly, and consider treatment with disease progression (i.e. meet intermediate-risk criteria, decrease in PSA doubling time <3 years, DRE changes, or prostate biopsy demonstrating Gleason score ≥7, >2 scores positive, >50% involvement in core sample). Curative options include brachytherapy and radical prostatectomy, which are preferred over external beam radiation
- **INTERMEDIATE RISK**—consider brachytherapy or radical prostatectomy for low intermediate risk group. LHRH agonist × 6 months combined with external beam radiation (starting at 3 months) for high intermediate risk group
- **HIGH RISK**—usually LHRH agonist × 2-3 years combined with external beam radiation (starting at 6–8 months)
- **RELAPSE**—may consider salvage (i.e. external beam radiation for patients with radical prostatectomy or brachytherapy) for young and fit patients. Otherwise, treat as advanced disease

ADVANCED DISEASE (T4, N1–3, M1)

- **FIRST LINE**—**life-long castration** (surgical or medical with LHRH agonists [*leuprolide* 22.5 mg IM q3month, *goserelin* 10.8 mg SC q3month] plus antiandrogen [*bicalutamide* 50 mg PO daily, *flutamide* 250 mg PO TID] for ≥7 days to prevent testosterone flare response). Note that up-front combined androgen blockade may be "considered" an option as per ASCO. Early initiation of androgen deprivation therapy may provide disease-specific survival but not overall survival benefit compared to starting treatment when patient become symptomatic, and thus not recommended
- **SECOND LINE**—consider **combined androgen blockade** with antiandrogen (*bicalutamide* 50 mg PO daily, *flutamide* 250 mg PO TID, nilutamide) added onto surgical/medical castration long term
- **THIRD LINE AND BEYOND**—consider antiandrogen withdrawal, ketoconazole, corticosteroids, diethylstillbestrol or treat as castration recurrent prostate cancer
- **CASTRATION RECURRENT PROSTATE CANCER**—if symptomatic, consider abiraterone acetate, enzalutamide, docetaxel, cabazitaxel (if failed docetaxel), or mitoxantrone. If asymptomatic, sipuleucel-T, abiraterone acetate, docetaxel or third line options are reasonable. Both symptomatic/asymptomatic patients should remain on LHRH agonist to potentially slow disease progression
- **BONE METASTASES**—bisphosphonates (zoledronic acid), radium-223, palliative radiation or radionuclide (strontium)

TREATMENT ISSUES

COMPARISON OF TREATMENTS FOR LOCALIZED DISEASE[a]

	Impotence	Urinary incontinence	Urinary irritation	GI irritation
Prostatectomy[b]	50–90%	10–20%	15–60%	2–17%
Brachytherapy	50%	1–2%	12–30%	10%
External RT[c]	50%	1–2%	2–30%	30%

[a]Side effects at 5 years are listed
[b]Symptoms tend to decrease over time
[c]Symptoms tend to increase over time

TREATMENT ISSUES (CONT'D)

RADICAL PROSTATECTOMY

- **BENEFITS**—5-year disease-free survival 85%
- **INDICATIONS**—preferred for patients with low-risk disease, life expectancy >20 years, or significant urinary symptoms
- **CONTRAINDICATIONS**—age >70, high-risk disease
- **ADVERSE EFFECTS**—urinary (frequency, urgency, nocturia, dysuria, incontinence), impotence

BRACHYTHERAPY—implant of radioactive seeds

- **BENEFITS**—5-year disease-free survival 96%
- **INDICATIONS**—eligibility criteria include PSA ≤15 ng/mL, Gleason score ≤7, stage ≤T2c, prostate volume ≤60 mL, and life expectancy >5 years
- **CONTRAINDICATIONS**—significant urinary symptoms (as prostate swells significantly shortly after procedure), prior TURP
- **ADVERSE EFFECTS**—urinary (frequency, urgency, nocturia, dysuria, incontinence), GI (diarrhea, tenesmus), and impotence; 3% require indwelling urinary catheter for >3 weeks and <1% chance of severe GI symptoms requiring colos-

TREATMENT ISSUES (CONT'D)

tomy. The symptoms typically peak at 6 weeks and generally resolve over time; 50% of patients return to baseline symptoms at 3 months and 95% by 1 year

EXTERNAL BEAM RADIATION

- **BENEFITS**—5-year disease-free survival 80%
- **INDICATIONS**—preferred for patients with high-risk disease or older
- **CONTRAINDICATIONS**—pelvic kidney, inflammatory bowel disease, connective tissue disease (SLE, scleroderma), or prior radiation to same region
- **ADVERSE EFFECTS**—urinary (frequency urgency, nocturia, dysuria, incontinence), GI (diarrhea, rectal bleeding), and impotence. Urethral stricture (1%), bowel obstruction (0.1%). Also risk of late-onset second malignancy

TREATMENT ISSUES (CONT'D)

LHRH AGONISTS

- **INDICATIONS**—high intermediate or high-risk localized disease, salvage setting, or advanced disease setting. Requires the use of an antiandrogen (flutamide) for first few weeks to counter testosterone flare response
- **ADVERSE EFFECTS**—fatigue, hot flushes, mood changes, weight gain, decreased libido, impotence, gynecomastia, and over the long-term decreased muscle mass, anemia, and osteoporosis. All patients initiated on LHRH agonists should have baseline bone density scan and be started on calcium and vitamin D supplements. Bisphosphonates should be given if osteoporosis confirmed by DEXA

TIME LINE—median time from castration to androgen independence 1.5 years. Median time from androgen independence to death 1.5 years

Testicular Cancer — EGCCCG Guidelines Ann Onc 2004 15

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY

- **TESTICULAR INTRAEPITHELIAL NEOPLASIA** (TIN)—70% chance of progression to testicular cancer in 7 years
- **GERM CELL TUMOR** (95%)—can differentiate into any immature or mature tissue type, usually mixed
  - **SEMINOMA** (40%)—neoplastic counterpart of spermatocyte. Age thirties to forties, pure, αFP negative and sometimes slightly βhCG positive. Few metastasize. Very chemo- and radiosensitive
  - **NON-SEMINOMA** (60%)—age twenties to thirties, pure or mixed, more metastasize. Chemosensitive. Include the following subtypes
    - **EMBRYONAL CELL CARCINOMA**—neoplastic counterpart of inner cell mass of embryo. May be βhCG+, αFP+
    - **YOLK SAC TUMOR**—neoplastic counterpart of yolk sac. Usually αFP+
    - **CHORIOCARCINOMA**—neoplastic counterpart of chorionic villus. Usually βhCG+
    - **IMMATURE TERATOMA**—neoplastic counterpart of fetal tissue. Marker negative
    - **MATURE TERATOMA**—neoplastic counterpart of mature adult tissue. Marker negative. Completely resistant to chemotherapy. May transform into malignant mesodermal, endodermal, or ectodermal elements

PATHOPHYSIOLOGY (CONT'D)

- **SEX CORD STROMAL TUMORS**
  - **SERTOLI CELL TUMOR**
  - **LEYDIG CELL TUMOR**
  - **GRANULOSA CELL TUMOR**
  - **MIXED CELL TYPE (SERTOLI–LEYDIG CELL)**
- **MIXED GERM CELL AND STROMAL TUMORS**
  - **GONADOBLASTOMA**
- **LYMPHOMA**
- **RHABDOMYOSARCOMA**
- **CARCINOID**

ISOCHROMOSOME 12P—characteristic of germ cell tumors. Poorly differentiated neoplasms of unknown primary with this cytogenetic feature are highly sensitive to cisplatin-based chemotherapy

RISK FACTORS

- **FAMILY HISTORY**—affected relatives
- **DISEASES**—prior testicular cancer, cryptorchidism (10–40×), testicular feminization syndromes, Klinefelter syndrome

CLINICAL FEATURES

LOCOREGIONAL—testicular mass ± pain, acute epididymitis (25% of embryonal cell tumor and mixed teratoma), back pain (10%), gynecomastia (βhCG), infertility (3%)

METASTATIC—dyspnea, cough, headaches, stroke

CONSTITUTIONAL—weight loss, anorexia, fatigue

STAGING

TNM STAGING (7TH EDITION)

T stage

- **T1** = limited to testis and epididymis without vascular/lymphatic invasion; tumor may invade into tunica albuginea but not tunica vaginalis
- **T2** = limited to testis and epididymis with vascular/lymphatic invasion or tumor extending through the tunica albuginea with involvement of the tunica vaginalis
- **T3** = invades the spermatic cord ± vascular/lymphatic invasion
- **T4** = invades the scrotum ± vascular/lymphatic invasion

N stage (pelvic → paraaortic LN)

- **N1** = 1 or more LNs, all ≤2 cm
- **N2** = 1 or more LNs between 2-5 cm
- **N3** = any LN >5 cm

M stage

- **M1a** = non-regional LN or lung
- **M1b** = sites other than non-regional LN or lung (e.g. bone)

SERUM MARKER DESIGNATION

	αFP (ng/mL)	βhCG (IU/L)	LDH
S1	<1000	<5000	<1.5×
S2	1000–10,000	5000–50,000	1.5–10×
S3	>10,000	>50,000	>10×

STAGE GROUPINGS

Stage	TNM @ = any
IA	T1N0M0S0
IB	T2–4N0M0S0
IS	T@N0M0S1–3
IIA	T@N1M0S0–1
IIB	T@N2M0S0–1
IIC	T@N3M0S0–1
IIIA	T@N@M1aS0–1
IIIB	T@N@M0–1aS2
IIIC	T@N@M0–1aS3, T@N@M1bS@

Risk group	Non-seminoma	Seminoma
Good (90% 5-year survival)	Testicular or retroperitoneal tumor, S1, and absence of non-pulmonary metastases	Any location, any marker, and absence of non-pulmonary metastases
Intermediate (80% 5-year survival)	Testicular or retroperitoneal tumor, S2, and absence of non-pulmonary metastases	Any location, any marker, and any non-pulmonary metastases
Poor (50% 5-year survival)	Testicular, retroperitoneal, or mediastinal tumor, S3, or non-pulmonary metastases	Not applicable

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, lipase, αFP, βhCG, LDH, TSH, T3, T4, total testosterone, LH, FSH
- **IMAGING**—testicular US, CXR, CT abd/pelvis, CT head (if advanced disease with intermediate or poor prognosis), bone scan (if suspect metastasis)
- **RADICAL INGUINAL ORCHIECTOMY**

SPECIAL

- **SEMEN ANALYSIS**—if fertility a consideration

DIAGNOSTIC AND PROGNOSTIC ISSUES

DIFFERENTIAL DIAGNOSIS OF TESTICULAR MASS—epididymitis, hydroceles, varicoceles, spermatoceles, inguinal hernias, orchitis (gummatous, tuberculous), hematoma, testicular torsion

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

TUMOR MARKERS—essential for diagnosis, staging, and monitoring treatment response

- **LDH**—less specific, indicates tumor bulk
- **βhCG**—elevated in trophoblastic tumor, choriocarcinoma. Half-life 1-3 days
- **αFP**—elevated in yolk sac tumor. Half-life 5-7 days

Tumor	βhCG	αFP
Non-seminoma	↑ in up to 85%	↑ in up to 80%
Seminoma	↑ in 15–25%	Normal

PROGNOSTIC FACTORS—vascular invasion is most important indicator for relapse in non-seminoma

MANAGEMENT

NOTE: all cases should be discussed with an interdisciplinary team experienced in the management of testicular cancer

EARLY SEMINOMA

- **STAGE I—orchiectomy** + one of adjuvant **radiation** (paraaortic/paracaval LN, 3–4% relapse) or adjuvant **carboplatin** (1–2 cycles, 3–4% relapse) or **surveillance** (15–20% relapse (higher risk of recurrence if >4 cm or rete testis involvement)
- **STAGE IIA—orchiectomy + radiation** (paraaortic/ipsilateral iliac LN, 6-year relapse-free survival 95%)
- **STAGE IIB—orchiectomy** + one of **radiation** (paraaortic/ipsilateral iliac LN, 6-year RFS 89%) or **chemotherapy** (if radiation not given, BEP × 3 or EP × 4, where B = bleomycin, E = etoposide, P = cisplatin)
- **STAGE IIC OR III**—BEP × 3 or EP × 4

EARLY NON-SEMINOMA

- **STAGE I WITH NO VASCULAR INVASION** (14–22% relapse)—**orchiectomy** + one of **surveillance** (14–22% relapse) or **chemotherapy** (if surveillance not chosen, BEP × 2) or nerve-sparing retroperitoneal [NSRP] **LN dissection** (if both surveillance and chemotherapy not chosen). Surveillance is recommended
- **STAGE I WITH VASCULAR INVASION** (48% relapse)—**orchiectomy** + one of **chemotherapy** (BEP × 2, 3% relapse) or **surveillance** (if chemotherapy not given, 48% relapse) or **NSRP-LN dissection** (if both surveillance and chemotherapy not chosen, 10% relapse). Surveillance is recommended
- **STAGE IIA, MARKER NEGATIVE—orchiectomy** + one of **NSRP-LN dissection** → if pathologic stage IIA or IIB, BEP × 2; if stage I, surveillance only, or **surveillance** (follow-up every 6 weeks) → if regression, follow-up only; if no change, NSRP-LN dissection or close follow-up; if progressive disease, BEP × 3 or NSRP-LN dissection

MANAGEMENT (CONT'D)

- **STAGE IIA, MARKER POSITIVE—orchiectomy + BEP × 3 + resection** if residual tumor
- **STAGE IIB—orchiectomy + BEP × 3 + resection** if residual tumor

ADVANCED SEMINOMA AND NON-SEMINOMA (IIC, IIIA-C)

- **GOOD RISK—orchiectomy + chemotherapy** (BEP × 3 or EP × 4)
- **INTERMEDIATE/POOR RISK—orchiectomy + chemotherapy** (BEP × 4)
- **RESIDUAL TUMOR POST-CHEMOTHERAPY—marker normalized** (proceed to resection → if necrosis (40%), differentiated teratoma (40%) or <10% viable tumors, follow-up only; if >10% viable tumors, consolidative chemotherapy with VIP × 2; if incomplete resection of viable tumor, treat as marker increased), **marker elevated but plateau** (follow-up 4–12 weeks → treat as marker normalized or marker increased depending on trend), **marker increased after short interval** (salvage chemotherapy with PEI × 4, VIP × 4, VeIP × 4, TIP × 4)
- **NOTE**—B = bleomycin, E/V = etoposide (VP16), P = cisplatin, I = ifosfamide, Ve = vinblastine, T = taxol

RELAPSED SEMINOMA—if systemic relapse, consider BEP × 4. If locoregional relapse, consider BEP or radiotherapy. Salvage chemotherapy regimens after first line chemotherapy include PEI × 4, VIP × 4, or VeIP × 4 or TIP × 4

RELAPSED NON-SEMINOMA—salvage chemotherapy regimens after first-line chemotherapy include VIP × 4, or VeIP × 4 or TIP × 4. For late relapses, patients with negative tumor markers should have immediate radical surgery. If unresectable disease, consider salvage chemotherapy and then resection if possible. If unresectable disease and localized, consider radiotherapy

TREATMENT ISSUES

GROWING TERATOMA SYNDROME—defined as enlargement of a residual mass post-chemotherapy, despite complete normalization of tumor marker suggesting eradication of malignant population. Surgical resection is indicated for a growing teratoma as it does not respond to chemotherapy or radiation and may transform into malignant tumors such as adenocarcinoma or rhabdomyosarcoma

RADICAL ORCHIECTOMY—should always be done prior to any further treatment, except for life-threatening metastatic disease in which chemotherapy should be given first

TREATMENT ISSUES (CONT'D)

ORGAN-PRESERVING SURGERY—should be done at experienced centers only. Consider if synchronous bilateral testis tumors, metachronous contralateral (second) testis tumor, or tumor in a solitary testis and sufficient endocrine function

FERTILITY ISSUES—consider cryoconservation before orchiectomy and testicular sperm extraction if bilateral orchiectomy. Testosterone replacement should be given if bilateral orchiectomy. Patients planning to father children should have hormone and semen analysis for 1- to 3-year post-treatment

Brain Tumors

See BRAIN TUMORS (p. 335)

Cancer of Unknown Origin

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY

- **ADENOCARCINOMA**—well to moderately differentiated (60%)
- **ADENOCARCINOMA/CARCINOMA**—poorly differentiated (30%)
- **SQUAMOUS CELL CARCINOMA** (5%)
- **UNDIFFERENTIATED NEOPLASMS** (5%)

NATURAL HISTORY—early, unpredictable, and aggressive metastasis. Primary too small to cause symptoms

Related Topic
Tumor Markers (p. 239)

IMMUNOHISTOCHEMICAL MARKERS

- **CARCINOMA**—cytokeratin negative, common leukocyte antigen, S100, vimentin negative. Breast cancer may be ER/PR positive
- **LYMPHOMA**—common leukocyte antigen
- **SARCOMA**—vimentin positive (mesenchymal), desmin positive (rhabdomyosarcoma), factor VII antigen (angiosarcoma)
- **MELANOMA**—S100, HMB 45, MART, vimentin, NSE positive
- **NEUROENDOCRINE TUMORS**—neuron-specific enolase, synaptophysin, chromogranin

PATHOPHYSIOLOGY (CONT'D)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, LDH, INR, PTT, β-hCG, AFP, PSA, Ca 125, CEA, CA 19–9
- **IMAGING**—CT chest/abd/pelvis
- **SPECIAL**—tissue biopsy

MANAGEMENT

TREAT UNDERLYING CAUSE—see table below for tailored treatment of cancer of unknown primary based on most likely tumor type

SUPPORTIVE—symptom control, consider palliative care consult

MANAGEMENT (CONT'D)

Presentation	Likely primary	Key history and physical	Investigations	Empiric treatment(s)
Poorly differentiated midline disease in young men	Germ cell tumor (testicular, retroperitoneal)	Gynecomastia suggests seminoma. Perform testicular examination	β-hCG, AFP. Look for isochromosome 12 which suggests tumor responsive to platinum-based therapy	Treat as germ cell tumor (BEP). Potentially curable
Squamous cell carcinoma with cervical lymphadenopathy	Head and neck cancer (hypopharynx, oropharynx, nasopharynx), skin, esophagus, lung	Smoker, alcohol use	Quadroscopy, CT chest, PET scan. Bronchoscopy and upper GI endoscopy may be considered. FNA first, then core biopsy if negative	Neck dissection and radiation. Potentially curable
Axillary lymphadenopathy in women	Breast cancer	Breast exam	Mammogram, US breast, MRI breast	Mastectomy with axillary dissection or whole breast irradiation, adjuvant chemotherapy. If lytic metastasis in postmenopausal women, consider hormonal treatment
Squamous cell carcinoma with inguinal lymphadenopathy	Cervical/rectal cancer	Pelvic exam, colposcopy	Anoscopy, sigmoidoscopy, CT abd/pelvis	Lymph node dissection, chemoradiation
Peritoneal carcinomatosis	Ovarian cancer variant, primary peritoneal cancer, metastasis from colorectal or stomach cancer	Pelvic exam	Colonoscopy, gastroscopy, CT abd/pelvis, CEA, CA-125 (ratio 1/20)	Treated as ovarian with carboplatin, paclitaxel
Liver metastasis	GI (colorectal [usually otherwise well], pancreatic, esophageal, gastric, hepatic [Orientals or cirrhosis], lung, breast	General	CEA, CA 19-9, CA 15-3, AFP, colonoscopy	Gemcitabine, pemetrexed
Lung nodule(s)	Metastasis (lower lobes, multiple), lung cancer (upper lobe, single)	Smoking history	CT chest	Platinum-based doublet chemotherapy
Malignant pleural effusion	Lung adenocarcinoma, mesothelioma	Smoking, asbestos exposure	Thoracentesis	Thoracentesis
Blastic bone metastasis	Prostate (most common), lung, breast	DRE	PSA, plain X-rays of bones, bone scan	Hormonal therapy if suspect prostate cancer

Tumor Markers

PATHOPHYSIOLOGY

DEFINITION—substances that can be measured quantitatively in the serum in order to detect a cancer and its organ of origin. May act as surrogate of tumor bulk

TYPES OF TUMOR MARKERS

- **TUMOR-SPECIFIC PROTEINS**—fusion gene product in CML (bcr–abl), monoclonal band in multiple myeloma
- **ONCOFETAL ANTIGENS** (non-specific)—expressed during embryological development and in cancer cells. Examples include CEA in all GI and some other tumors, AFP in hepatocellular carcinoma and germ cell tumor, and CA 125 in ovarian cancer
- **OVER-EXPRESSED PROTEINS** (non-specific)—present in normal differentiated cells but lesser amount. Examples include PSA in prostate cancer and CA 15-3 in breast cancer

UTILITY OF TUMOR MARKERS—screening, diagnosis, prognosis, monitor response to treatment, monitor recurrence (after adjuvant therapy)

PROSTATE SPECIFIC ANTIGEN (PSA)

NORMAL RANGE—< 4 ng/mL (age-dependent range: 40–49 years old <2.5 ng/mL, 50–59 years old <3.5 ng/mL, 60–69 years old <4.5 ng/mL, 70–79 years old <6.5 ng/mL)

ELEVATED—prostate cancer, BPH, prostatitis, perineal trauma (including catheterization), endoscopy, prostate biopsy, recent DRE or ejaculation

UTILITY IN PROSTATE CANCER

- **SCREENING**—varying guidelines for using PSA for screening; always discuss risks and benefits (including false positives and negatives) with patients. If proceeding, start at age 50 for men with life expectancy >10 years. Perform PSA annually if PSA >1 ng/mL, and every 4 years if PSA <1 ng/mL. Combine with annual DRE
- **DIAGNOSIS, PROGNOSIS, RESPONSE, FOLLOW-UP FOR RELAPSE**—extremely useful. See PROSTATE CANCER for more details (p. 231)

CARCINOEMBRYONIC ANTIGEN (CEA)

NORMAL RANGE—< 4 μg/L (<5 μg/L for smokers)

ELEVATED—colorectal cancer (sens <25% in early cancer and 75% in advanced cancer), gastric cancer (sens 50%), pancreatic cancer (sens 50%), breast cancer (sens 40–73%), lung cancer (sens 77%), ovarian cancer, IBD (4–10 μg/L), cirrhosis, hepatitis, pancreatitis, peptic ulcer disease, smoking (sens 19%), chronic lung disease, hypothyroidism, normal (sens 3%)

CARCINOEMBRYONIC ANTIGEN (CEA) (CONT'D)

UTILITY IN COLORECTAL CANCER

- **PROGNOSIS**—CEA >5 μg/L may correlate with poorer prognosis
- **ADJUVANT SETTING**—elevated postoperative CEA implies the presence of persistent disease and requires further evaluation. For stage II and III disease post-resection, CEA levels should be performed every 3 months for at least 3 years if the patient is a potential candidate for surgery or chemotherapy for metastatic disease (even if previously CEA negative)
- **METASTATIC SETTING**—CEA is the marker of choice for monitoring the response of metastatic disease to systemic therapy

CA 19–9

NORMAL RANGE—< 37 kU/L

ELEVATED—pancreatic cancer (sens 70–90%, spc 80–90%), cholangiocarcinoma, colorectal cancer (sens 20–40%), gastric cancer (sens 20–40%), ovarian cancer, pancreatitis, liver failure

UTILITY IN PANCREATIC CANCER

- **DIAGNOSIS**—level >120 kU/L is suggestive of malignancy. Level >1000 kU/L predicts metastatic disease (PPV of 97%)
- **RESECTABLE DISEASE**—elevated CA19-9 postoperatively may predict for recurrent disease
- **LOCALLY ADVANCED OR METASTATIC DISEASE**—elevations in serial CA 19-9 suggest progressive disease but confirmation with other studies needed

CA 15-3

NORMAL RANGE—< 28 kU/L

ELEVATED—breast cancer (sens for stage I 5–30%, stage II 15–50%, stage III 60–70%, stage IV 65–90%), ovarian cancer (46%), lung cancer (26%), liver cancer (30%)

UTILITY IN BREAST CANCER

- **DIAGNOSIS**—may be used sometimes to determine the presence of metastatic disease. 86 kU/L + history of breast cancer strongly suggests metastasis
- **METASTATIC SETTING**—may be used to suggest treatment failure, particularly if disease is not readily measurable

CA 125

NORMAL RANGE—< 35 kU/L

ELEVATED—epithelial ovarian cancer (sens 50% in stage I, 85% in all), breast cancer, colorectal cancer, pancreatic cancer, lung cancer, endometrial cancer, benign ovarian tumors (sens 26%), ascites, peritonitis, pelvic inflammatory disease, cirrhosis, menstruation, endometriosis, salpingitis, fibroids, right-sided heart failure, first trimester pregnancy

UTILITY IN EPITHELIAL OVARIAN CANCER

- **SCREENING**—may have a role in early detection of ovarian cancer in women with hereditary ovarian cancer syndrome in combination with transvaginal ultrasound
- **DIAGNOSIS**—in postmenopausal women with asymptomatic palpable pelvic masses, CA 125 > 65 kU/L has PPV of 90% for ovarian cancer
- **PROGNOSIS**—rate of decrease in CA 125 after cytoreductive surgery and during cytotoxic chemotherapy has prognostic value
- **RESPONSE**—useful for following disease response during cytotoxic chemotherapy

CA 125 (CONT'D)

- **ADJUVANT SETTING**—every 3 months for 2 years. However, limited treatment for relapsed disease limits clinical value of detection

TUMOR MARKERS IN EVERYDAY PRACTICE

Tumor type	Tumor marker
Prostate	PSA
Colorectal (GI)	CEA, CA 19-9
Pancreas	CA 19-9, CEA
Liver	αFP
Breast	CA 15-3, CEA, CA 125, CA 27.29
Ovary	CA 125, CA 15-3, CA 19-9, CEA
Lung	CEA, CA 19-9, CA 125, LDH
Germ cell tumor	αFP, βhCG, LDH
GTN	βhCG
Carcinoid tumor	Chromogranin, 5-HIAA
Non-Hodgkin's	LDH
Hodgkin's	ALP
Myeloma	M-protein, β2 microglobulin

UTILITY OF SPECIFIC TUMOR MARKERS

Tumor marker	Tumor type	Screen	Diagnosis	Prognosis	Response	Follow-up (recurrence)
PSA	Prostate	?	✓	✓	✓	✓
CEA	Colorectal	×	×	✓	✓	✓
CA 19–9	Pancreas	×	×?	×	✓?	✓?
CA 15–3	Breast	×	×	×	M	×
CA 125	Ovary	×?	×?	✓	✓	✓?
αFP	Germ cell	×	✓	✓	✓	✓
	Liver	×?	✓	✓	✓	×
βhCG	Germ cell	×	✓	✓	✓	✓
	GTN	×	✓	✓	✓	✓
LDH	Germ cell	×	✓	✓	✓	✓
	Lymphoma	×	×	✓	✓	×

✓ useful, ? controversial, x not useful, *M* metastatic setting only

Cancer Screening

Canadian Association of Gastroenterology Guidelines for Colon Cancer Screening 2004 NEJM 2009 361:12

PRINCIPLES OF SCREENING

GOAL—screening itself does not diagnose disease, but triggers investigations that lead to diagnosis. Early diagnosis in asymptomatic patients would allow early intervention which could lead to improved outcome. Up to 35% of cancer deaths may be prevented by early detection

PRINCIPLES OF SCREENING (CONT'D)

CRITERIA FOR SCREENING

- **DISEASE**—major cause of death, high prevalence, natural history from latency to overt disease well characterized, treatment available and beneficial

PRINCIPLES OF SCREENING (CONT'D)

- **TEST**—acceptable to population (easy to administer, minimal discomfort), cost-effective, high specificity (key) and sensitivity. Prefer high sensitivity if serious and highly treatable or infectious disease, or subsequent diagnosis cheap and easy. May sacrifice sensitivity for specificity if high cost of subsequent testing
- **PATIENTS**—life expectancy >10 years, lack of significant comorbidities (screening may alter their clinical outcome)

CHALLENGES WITH SCREENING TRIALS

- **PATIENT POPULATION**—healthy individuals instead of patients (less motivated)
- **STUDY DESIGN**—longer duration of follow-up, larger sample size, more expensive
- **SURROGATE ENDPOINTS**—cancer incidence, dysplasia, polyps instead of survival

BIASES ASSOCIATED WITH SCREENING TRIALS

- **VOLUNTEER BIAS**—volunteers tend to have better health and lower mortality rate
- **LEAD TIME BIAS**—screening may allow disease to be detected earlier (asymptomatic) than when it would have been detected due to symptoms. Thus, people with disease detected by screening may appear to have longer overall survival. To correct for this, should compare not the length of survival from diagnosis to death, but rather the age-specific death rates. Alternatively, estimate the lead time and take it into account
- **LENGTH BIAS**—disease detected by screening may have a more indolent course, and thus more favorable prognosis. May control for this by comparing the experience of screened and symptom-detected cases at subsequent screening examinations

SCREENING FOR SPECIFIC CANCERS

- **BREAST**—self-breast examination, clinical breast examination, mammography
- **CERVICAL**—Pap smear, HPV DNA
- **LUNG**—low dose CT chest for patients aged 55-77 with at least a 30 pack year history who are either current smokers or quit within the last 15 years
- **COLORECTAL**—fecal occult blood (FOB), fecal immunochemical test (FIT) sigmoidoscopy, double-contrast barium enema, colonoscopy, CT colonography
- **PROSTATE**—DRE, PSA
- **OVARIAN**—US, CA125
- **GASTRIC**—gastroscopy (Asia)

underlined = good evidence to support screening

PROSTATE CANCER SCREENING

DIGITAL RECTAL EXAMINATION (DRE)—no survival benefit demonstrated

PROSTATE-SPECIFIC ANTIGEN (PSA)—see tumor markers (p. 239). Evidence for survival benefit conflicting

OVERALL—for men who have life expectancy >10 years and who desire screening after extensive counseling on the risks and benefits, consider PSA testing starting at age 50. Perform PSA annually if PSA >1 ng/mL and every 4 years if PSA <1 ng/mL. Combine with annual DRE

Related Topics
Tumor Markers (p. 239)
Hereditary Cancer Syndromes (p. 243)

COLON CANCER SCREENING

FLEXIBLE SIGMOIDOSCOPY—case–control studies demonstrated 60–80% reduction in mortality. Potential survival benefit. Negative test in 75–93% of cases (30–65% negative even with advanced polyp) → repeat in 5 years; positive in 7–25% → proceed to colonoscopy

COLONOSCOPY—case–control studies demonstrated 50% reduction in mortality. Potential survival benefit. Negative test (i.e. no adenomatous polyps) in 50–80% of cases (2–12% negative even with advanced polyp) → repeat in 10 years; positive (i.e. ≥1 polyp) in 20–50% → repeat colonoscopy depending on findings

DOUBLE-CONTRAST BARIUM ENEMA—insufficient evidence to support benefit

CT COLONOGRAPHY—for polyps >10 mm, sens 85–93%, and spc 97%; for polyps 6–9 mm, sens 70–86%, and spc 86–93%. After detection of polyp, patient would need to undergo optical colonoscopy (ideally on standby) for resection. Risk of radiation exposure

FECAL OCCULT TEST (FOB)—detects peroxidase in blood. Rehydrated stool samples have been shown to reduce colorectal cancer mortality by 33% after 13 years if done annually and 21% after 18 years if done biennially; non-rehydrated stool samples have been shown to reduce colorectal cancer mortality by 18% after 18 years if done biennially. Negative test in 90–98% of cases (15–50% negative even with cancer) → repeat in 1–2 years; positive in 2–10% → proceed to colonoscopy

FECAL IMMUNOCHEMICAL TEST (FIT)—detects human globin. More specific and less sensitive than FOB

COLON CANCER SCREENING (CONT'D)

STOOL DNA TEST (sDNA)—need to provide entire stool sample. To be used in conjunction with colonoscopy

OVERALL APPROACH

- **AVERAGE RISK**—start screening at age 50 with *one* of colonoscopy every 10 years, flexible sigmoidoscopy every 5 years, FOB or FIT every 1–2 years, or double-contrast barium enema every 5 years. Both FOB and FIT detect primarily cancer, while the rest detect mostly polyps (i.e. earlier stage and thus preferred). Insufficient data to recommend routine CT colonoscopy or stool DNA testing
- **POLYPS ON COLONOSCOPY**—1–2 tubular adenomas → colonoscopy in 5 years; >2 adenomas → colonoscopy in 3 years; incomplete exam, numerous polyps, advanced adenoma, large sessile adenoma → repeat colonoscopy based on clinical judgment
- **POSITIVE FAMILY HISTORY**—one first-degree relative with cancer or adenomatous polyp at age <60 or two or more first-degree relatives with cancer or adenomatous polyp at any age → colonoscopy every 5 years beginning at 40 or 10 years earlier than youngest index case (whichever first)
- **HNPCC, FAP, OR ATTENUATED ADENOMATOUS POLYPOSIS COLI (AAPC)**—genetic counseling and special screening. For HNPCC, colonoscopy every 1–2 years starting at 20–25 or 10 years earlier than youngest index case in family (whichever first); for FAP, colonoscopy annually beginning at 10–12 years of age AND upper endoscopy with both end- and side-viewing instruments to screen for duodenal/ampullary adenomas at 25-30 years. For AAPC, colonoscopy annually beginning at 16–18 years of age
- **IBD** (ulcerative colitis or Crohn's disease)—staging colonoscopy 8–10 years after diagnosis; screening interval should decrease with increasing duration of disease (variable). Annual colonoscopy for any patient with PSC (starting at diagnosis)

BREAST CANCER SCREENING

BREAST SELF-EXAMINATION (BSE)—no survival benefit demonstrated on its own and not recommended in general

CLINICAL BREAST EXAMINATION (CBE)—usually combined with mammography in studies

MAMMOGRAPHY—sensitivity 16–40%. Meta-analysis showed 20–30% relative risk reduction (RRR) in breast cancer mortality for women 50–69, 17% reduction for women 40–49, and inconclusive for women aged 70–74

BREAST CANCER SCREENING (CONT'D)

BREAST MRI—sensitivity 77–100% for breast cancer but not very specific and less sensitive than mammography in detecting DCIS. Studies only in high-risk women. No survival benefit demonstrated

BREAST US—may represent an alternative in women with dense breasts and increased risk of breast cancer who cannot tolerate MRI. No survival benefit demonstrated

OVERALL—mammogram should be done every 1–2 years for women aged 40-50 or greater for as long as women is in good health. Breast MRI should be considered for patients at high risk of developing breast cancer (e.g. BRCA carriers, Li–Fraumeni, previous chest irradiation)

OVARIAN CANCER SCREENING

CA125—elevated in 80% of women with advanced ovarian cancer, <50% of stage I ovarian cancer, and 1–2% of normal population. Low specificity

TRANSVAGINAL US—sensitivity 85% with PPV of 27% for women over age 50 at average risk and those over age 25 with family history of ovarian cancer

OVERALL—routine screening for average risk individuals not recommended. For those at high risk (family history, BRCA mutation), the decision should be individualized and may consist of transvaginal US and CA 125 every 6 months starting at age 35 or 5–10 years earlier than the youngest age at diagnosis in the family

CERVICAL CANCER SCREENING

PAP SMEAR—50–60% reduction in mortality if done every 1–3 years in women aged 18 and greater. Sensitivity and specificity for CIN2 and CIN3 are 55 and 97%, respectively

BETHESDA SYSTEM OF REPORTING CERVICAL CYTOLOGIC DIAGNOSIS

- **SQUAMOUS CELL**—atypical squamous cells of undetermined significance (ASC-US); atypical squamous cells cannot exclude HSIL (ASC-H)
- **LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION** (LSIL)—encompassing human papillomavirus, mild dysplasia, cervical intraepithelial neoplasia (CIN) 1
- **HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION** (HSIL)—encompassing moderate and severe dysplasia, carcinoma in situ, CIN2 and CIN3
- **SQUAMOUS CELL CARCINOMA**
- **GLANDULAR CELL**—atypical glandular cells (AGC), atypical glandular cells, favor neoplastic, endocervical adenocarcinoma in situ (AIS), adenocarcinoma

CERVICAL CANCER SCREENING (CONT'D)

HPV DNA TESTING—for high-risk serotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68). Sensitivity and specificity for CIN2 and CIN3 are 95 and 94%, respectively

OVERALL—routine screening for cervical cancer every 3 years for women aged 25 to 69. For women aged ≥70 who have previous adequate screening (3 successive negative Pap tests in last 10 years), screening may stop. If inadequate screening, continue until 3 negative test results. For women aged 30-65, may combine with HPV testing every 5 years

Hereditary Cancer Syndromes

HALLMARKS OF HEREDITARY CANCER

YOUNGER AGE
≥2 PRIMARY CANCERS
≥2 GENERATIONS

HALLMARKS OF HEREDITARY CANCER (CONT'D)

≥2 FIRST- OR SECOND-DEGREE RELATIVES (same side of family)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE A FAMILY HISTORY OF CANCER?

	Sens	Spc	LR+	LR–
Accuracy of self – reported family history of cancer in a first – degree relative by healthy individuals				
Colon cancer	53 – 86%	92 – 99%	23	0.25
Breast cancer	82%	91%	8.9	0.20
Endometrial ca	33%	98%	14	0.68
Ovarian cancer	50%	99%	34	0.51
Prostate cancer	70%	94%	12.3	0.32
Accuracy of self – reported family history of cancer in a first – degree relative by cancer patients				
Colon cancer	57 – 90%	96 – 99%	23	0.29
Breast cancer	85 – 98%	96 – 99%	41	0.07
Endometrial ca	29 – 56%	97 – 98%	20	0.55
Ovarian cancer	67 – 83%	96 – 99%	44	0.21
Prostate cancer	69 – 79%	93 – 99%	24	0.21

HEREDITARY NON-POLYPOSIS COLON CANCER (HNPCC) GENETIC TESTING CRITERIA (FOR PREMENOPAUSAL WOMEN ≤50 YEARS)

1. at least three relatives must have a cancer associated with HNPCC (colon, endometrial, ovarian, stomach, small bowel, hepatobiliary, ureter, renal pelvis, brain)
2. one should be a first-degree relative of the other 2. At least two successive generations should be affected
3. at least one of the relatives with cancer associated with HNPCC should have received the diagnosis before age 50 years

HEREDITARY BREAST/OVARIAN CANCER GENETIC TESTING CRITERIA

1. two breast cancers in a first- or second-degree relative and mean age at diagnosis of 40 years
2. one breast cancer and one ovarian cancer in a first- or second-degree relative and mean age at diagnosis of 41–50 years
3. two or more breast cancers and one ovarian cancer in a first- or second-degree relative
4. ovarian cancer in two relatives

APPROACH—"patient-reported family cancer histories for first-degree relatives are accurate and valuable for breast and colon cancer risk assessments. Negative family history reports for ovarian and endometrial cancers are less useful, although the prevalence of these malignancies within families is low"

JAMA 2004 292:12

BRCA SYNDROMES

	BRCA1	BRCA2
Genetics	Autosomal dominant with variable penetrance, 17q21	Autosomal dominant with variable penetrance, 13q13
Pathophysiology	Tumor suppressor, granin protein family with zinc finger motif, packaging and export of peptide hormones	Tumor suppressor
Cancer types	Breast (19% by age 40, 50% by age 50, 85% by age 70), ovarian (14–45% lifetime risk), prostate (8–16%), colon (6%)	Breast (50–85%), ovarian (<20%), male breast (6%), prostate (8–16%)
Clinical features	Young age of breast cancer, bilateral breast cancer, ER – (70%), lobular	Young age of breast cancer, bilateral breast cancer, male breast cancer, lobular
Genetic testing	2 common mutations	1 common mutation
Surveillance	Breast—starting at young age, clinical breast exam, mammogram, and MRI q6months Ovarian—screening decision individualized (consider transvaginal US ± CA-125)	
Prophylaxis	**Prophylactic mastectomy**—breast cancer risk reduction of 90% **Prophylactic oophorectomy**—when childbearing is complete. Breast cancer risk reduction of 75% and ovarian cancer risk reduction of 95% **Hormonal**—tamoxifen or raloxifene are not routinely recommended, especially in BRCA1 families, where the majority of cancers are ER negative	

LI–FRAUMENI SYNDROME

GENETICS—autosomal dominant
PATHOPHYSIOLOGY—tumor suppressor, p53 mutation
CANCER TYPES—soft-tissue sarcoma, osteosarcoma, leukemia, breast, melanoma, colon, pancreas, adrenal cortex, brain

VON HIPPEL–LINDAU SYNDROME

PATHOPHYSIOLOGY—VHL mutation
CANCER TYPES—hemangioblastomas of the brain, spinal cord, retina, renal cysts, and clear cell renal cell carcinoma (40%), pheochromocytomas, endolymphatic sac tumors of the middle ear, serous cystadenomas and neuroendocrine tumors of the pancreas, papillary cystadenomas of the epididymis and broad ligament

HEREDITARY MALIGNANT MELANOMA

CANCER TYPES—melanoma, pancreatic

HEREDITARY DIFFUSE GASTRIC CANCER (HDGC)

PATHOPHYSIOLOGY—E-cadherin gene CDH1 mutation
CANCER TYPES—diffuse signet ring cell type gastric, colon, breast (lobular), prostate, ovary

HEREDITARY NON-POLYPOSIS COLORECTAL CANCER (HNPCC, LYNCH SYNDROME)

GENETICS—autosomal dominant
PATHOPHYSIOLOGY—DNA mismatch repair genes (hMLH1, hMSH2, hPMS1, hPMS2, hMSH6). MSH2 and MLH1 account for most of the mutations
CANCER TYPES—colorectal (70–80% lifetime risk), endometrial (most common extracolonic

HEREDITARY NON-POLYPOSIS COLORECTAL CANCER (HNPCC, LYNCH SYNDROME) (CONT'D)

cancer in women), small bowel, gastric, ovarian, hepatobiliary, pancreatic, kidney, ureter, brain (Turcot's syndrome), skin (sebaceous adenomas ± keratoacanthomas in the Muir–Torre variant syndrome)

FEATURES—for colon cancer, predominant involvement of right colon, poorly differentiated, increased frequency of mucinous and signet cell tumors, lymphocytic infiltration, MSI high (90%), and better prognosis. Clinical diagnosis can be made by the Amsterdam criteria ★**321**★: ≥**3** relatives with colorectal cancer (two of whom must be first-degree relatives), ≥**2** generations involved, and ≥**1** family member diagnosed before age 50. FAP should be excluded

SURVEILLANCE—for individuals who have a mismatch repair gene mutation or are strongly suspected of having Lynch syndrome, consider colonoscopy every 1–2 years starting at 20–25 or 10 years earlier than the youngest age of colon cancer diagnosis in the family (start at age 30 for MSH6 mutations) and annually after age 40. Annual screening for endometrial and ovarian cancer (pelvic examination, endometrial aspirate, transvaginal US) beginning at age 30–35 years or 5–10 years earlier than the earliest age of first diagnosis of these cancers in the family. Median age of diagnosis is 48. Annual urinalysis and cytologic examination beginning at age 25–35. Annual skin surveillance. Periodic upper endoscopy should be considered

PROPHYLAXIS—total or subtotal colectomy with ileorectal anastomosis for HNPCC patients

HEREDITARY NON-POLYPOSIS COLORECTAL CANCER (HNPCC, LYNCH SYNDROME) (CONT'D)

with colorectal cancer or advanced adenoma (and post-surgical rectal surveillance). Discussion of prophylactic hysterectomy and salpingo-oopherectomy at around age 35 or at the end of childbearing

FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

GENETICS—autosomal dominant, 5q21–q22

PATHOPHYSIOLOGY—adenomatosis polyposis coli (APC) gene, a tumor suppressor gene that normally prevents accumulation of β-catenin by facilitating its phosphorylation and resultant degradation. One third of patients have no family history (new germline APC mutations or due to MYH gene mutations)

CANCER TYPES—colorectal (risk approaches 100% by age 45), duodenal, ampullary, gastric, follicular or papillary thyroid, hepatoblastoma, medulloblastoma (Turcot's syndrome)

FEATURES—colon polyps (more than 100), duodenal adenomatous polyps, extraintestinal manifestations (Gardner's syndrome) such as desmoid tumors, sebaceous or epidermoid cysts, lipomas, osteomas, supernumerary teeth, gastric polyps, and juvenile nasopharyngeal angiofibromas

SURVEILLANCE (all at-risk family member)—sigmoidoscopy or colonoscopy annually starting age 10–12. Upper endoscopy with end- and side-viewing endoscopes. Annual thyroid palpation

PROPHYLAXIS—total proctocolectomy at time of diagnosis in patients with multiple large (>1 cm) adenomas or adenomas with villous histology and/or high-grade dysplasia

Antineoplastic Agents

Chemotherapeutic agents	Activity[a]	Myelo. supp.	Emetogenic risk	Alopecia	Other major toxicities[b]	Dose modification[c]
Alkylating agents						
Bendamustine (IV)	CLL, NHL	++	++	+	LFT, 2nd malignancies, sterility	Renal, hepatic
Busulfan (IV)	BMT	+++	+	++	Pulmonary, seizures	Renal
Carmustine (BCNU, IV, wafer)	CNS, NHL	+++	+++	+	Pulmonary, renal, muco, diarrhea, LFT	Renal
Chlorambucil (PO)	CLL, HL, NHL	++	-	+	Mucositis, sterility	–
Cyclophosphamide (Cytoxan, IV/PO)	ALL, AML, CLL BR, GYN, NHL, BMT	+++	++(+)	+++	**Hemorrhagic cystitis**, muco, sterility, 2nd malignancies, cardiotoxicity	Renal, hepatic
Dacarbazine (DTIC, IV)	HL, melanoma, SA	++	+++	+	Flu-like symptoms, LFT, photo	Renal, hepatic
Ifosfamide (IV)	T, SA, NHL,	+++	++	+++	**Hemorrhagic cystitis**, neuro	Renal, hepatic
Lomustine (CCNU, PO)	CNS, NHL	+++	+	++	Pulmonary, renal, muco, diarrhea, LFT	Renal
Melphalan (PO)	MM, BMT, OV	++	+	+	Mucositis, sterility, 2nd malignancies	Renal
Streptozocin (IV)	Carcinoid, islet cell	+	+++	+	**Renal**, diarrhea, LFT, hypoglycemia	Renal
Temozolomide (PO)	CNS, melanoma	++	++	+	Photosensitivity	Renal, hepatic
Antimetabolites						
Capecitabine (xeloda, PO)	GI, BR	++	+	+	Muco, **diarrhea**, LFT, hand–foot, neuro	Renal
2-Chlorodeoxyadenosine (cladribine, IV)	NHL, hairy cell leukemia	+++	+	+	Constipation, fever, neuro, renal	–
Clofarabine (IV)	ALL	+++	++	+	Rash, hand-foot, LFT	Renal, hepatic
Cytosine arabinoside (Ara-C, IV)	ALL, HL, CML, AML, leptomeningeal	+++	+(+)	++	Mucositis, diarrhea, **cerebellar**	Renal, hepatic, neuro
Decitabine (IV)	MDS, CML	+++	+	+	diarrhea	–
Fludarabine (IV, PO)	NHL, CLL	++	++	+	Neuro, AIHA, LFT	Renal
5-Fluorouracil (IV)	GI, BR	+	+	++	Muco, **diarrhea**, hand–foot, cerebellar	Hepatic
Gemcitabine (IV)	GI, LU, BR, NPC, OV, bladder	++	+	++	Diarrhea, LFT, flu-like, rash	Renal, hepatic
Hydroxyurea (PO)	AML, CML	++	+	+	Mucositis, rash, LFT, 2nd malignancies	Renal

Antineoplastic Agents (cont'd)

Chemotherapeutic agents	Activity[a]	Myelo. supp.	Emetogenic risk	Alopecia	Other major toxicities[b]	Dose modification[c]
6-Mercaptopurine (6- MP, IV)	ALL	++	+	+	Mucositis, diarrhea, LFT	Renal, hepatic
Methotrexate (IV/PO)	ALL, BR, chorio, leptomeningeal	++	+	+	**Muco**, diarrhea, LFT, **renal**, pulm, neuro	Renal, hepatic
Nelarabine (IV)	CLL, TCL	+++	+	+	Neuro	Hepatic
Pemetrexed (IV)	LU, mesothelioma, BR	++	+	+	**Mucositis**, diarrhea, hand–foot, LFT, rash	Renal
Raltitrexed (IV)	GI, BR	++	+	+	Mucositis, diarrhea, LFT, **fatigue**	Renal
6-Thioguanine (6-TG, PO)	AML, ALL, CML	++	+	+	Mucositis, diarrhea, LFT	Hepatic
Topoisomerase inhibitors						
Daunorubicin (IV)	AML, ALL	+++	++	+++	**Cardiac**	Hepatic
Doxorubicin (hydroxydaunomycin, IV)	AML, ALL Bladder, BR, HL, NHL, SA, OV	+++	++	+++	**Cardiac**, 2nd malignancies	Hepatic
Doxorubicin (liposomal, IV)	KS, OV, MM, BR	++	+	+++	**Cardiac**, infusion, skin	Hepatic
Epirubicin (IV)	BR	+++	++	+++	Cardiac	Hepatic
Etoposide (IV/PO)	LU, T, NHL	++	+(+)	+++	Neuro, LFT	Hepatic, renal
Idarubicin (IV)	AML	+++	++	+++	Cardiac (less)	Hepatic, renal
Irinotecan (IV)	GI, LU, GYN, CNS	++	++	+++	**Diarrhea**, constipation, fever	Hepatic
Mitoxantrone (IV)	AML, BR, prostate	++	+	++	Cardiac, LFT	Hepatic
Topotecan (IV/PO)	OV, LU	+++	+	+++	Diarrhea, constipation, fever	Hepatic, Renal
Platinating agents						
Carboplatin (IV)	Bladder, LU, H&N, OV, T	++	++	+	Renal, neuro, ototoxicity (less)	Renal
Cisplatin (IV)	Bladder, LU, H&N, OV, T	++	+++	+	**Renal**, **neuro**, **ototoxicity**	Renal, neuro
Oxaliplatin (IV)	GI	+	++	+	**Neuro**, diarrhea	Neuro, renal
Antimicrotubular agents						
Albumin bound paclitaxel (Abraxane, IV)	BR, GI, LU	++	+	+++	Neuro, LFT	Hepatic

Antineoplastic Agents (cont'd)

Chemotherapeutic agents	Activity[a]	Myelo. supp.	Emetogenic risk	Alopecia	Other major toxicities[b]	Dose modification[c]
Cabazitaxel (IV)	Prostate	++	+	+	Diarrhea, nausea, neuropathy, edema, Infusion r'xn	Hepatic
Docetaxel (taxotere, IV)	BR, GI, H&N, LU, OV, prostate	++	+	+++	Neuro, nails, myalgia, arthralgia, **edema**	Hepatic
Eribulin (IV)	BR	++	+	++	Neuro, cardiac, LFT	Hepatic, renal
Ixabepilone (IV)	BR	++	+	+	Neuro	Hepatic
Paclitaxel (taxol, IV)	BR, LU, ~~prostate~~, OV	++	+	+++	Neuro, nails, myalgia, arthralgia	Hepatic, neuro
Vinblastine (IV)	NHL, T	++	+	++	Cramps, neuro, constipation	Hepatic, neuro
Vincristine (oncovin, IV)	ALL, NHL, SA	–	+	++	**Neuro**, constipation	Hepatic, neuro
Vinorelbine (navelbine, IV)	LU, BR	++	+	+++	Neuro, constipation, diarrhea	Hepatic
Others						
Bleomycin (IV)	Testicular, NHL	+	+	++	Pulmonary, hemorrhagic cystitis	Renal
Mitomycin C (IV)	GI, BR, GU	+++	+	+	Pulmonary, HUS, GU irritation	Renal

Antineoplastic Agents (cont'd)

Hormonal LHRH agonists	Activity[a]	Cytopenia	Other major toxicities[b]
Goserelin (Zoladex) (SQ, implant)	Prostate, BR	–	Hot flashes, mood changes, sexual dysfunction, diarrhea, anemia,
Leuprolide (Lupron) (IM, SQ)	Prostate, BR	–	loss of muscle mass, osteoporosis
Selective estrogen receptor modulators			
Tamoxifen (Nolvadex)	BR	–	Hot flashes, mood Δ, vaginal dryness/discharge, thromboembolism, hypercalcemia, endometrial cancer
Aromatase inhibitors			
Anastrozole (Arimidex)—non-steroidal (PO)	BR	–	Hot flashes, mood Δ, arthralgia, vaginal dryness and discharge,
Letrozole (Femara)—non-steroidal (PO)	BR	–	osteoporosis for all aromatase inhibitors
Exemestane (Aromasin)—steroidal (PO)	BR	–	
Other hormonal agents			
Abiraterone (Zytiga)—inhibits CYP-17 (PO)	Prostate	–	HTN, hyperkalemia, edema, LFT's, arthralgias, hot flashes
Bicalutamide (Casodex)—anti-androgen (PO)	Prostate	–	Hot flashes, mood changes, sexual dysfunction, diarrhea, anemia,
Enzalutamide (Xytandi)—blocks androgen receptor (PO)	Prostate	+	Seizures, fatigues, hot flashes
Finasteride (Proscar)—5-α reductase inhibitor (PO)	Prostate	–	Postural hypotension, sexual dysfunction, dizziness
Flutamide (Eulexin)—antiandrogen (PO)	Prostate	–	Loss of muscle mass, osteoporosis
Fulvestrant (Faslodex)—ER blocker (IM)	BR	–	Hot flashes, nausea, diarrhea, back pain, pharyngitis
Megestrol (Megace)—progestin (PO)	BR, endometrial	–	Vaginal bleed and irregularities, nausea, weight gain, thromboembolism

Antineoplastic Agents (cont'd)

Targeted agents	Activity[a]	Cytopenia	Other major toxicities[b]
Monoclonal antibodies			
Ado-trastuzumab emtansine (Kadcyla)—anti-HER2 (IV)	BR	-	Cardiomyopathy, ophthalamic, LFT's
Alemtuzumab (Campath)—anti-CD52 (SC/IV) *withdrawn, to be relaunched as Lematra	NHL, TCL	+++	Infusion rx'n, infections (e.g. CMV, HSV, TB, fungal), pancytopenia
Bevacizumab (Avastin)—anti-VEGF (IV)	GI, CNS, LU, RC	-	Infusion rx'n, HTN, bleed, thrombosis, GI perforations, proteinuria
Brentuximab (Adcetris)—anti CD-30 (IV)	HL, NHL	++	Neuro, infusion reactions, nausea, fatigue, arthralgias
Cetuximab (Erbitux)—anti-EGFR (IV)	GI, H&N	-	Infusion rx'n, rash, nail/hair changes, mucositis, diarrhea, hypomagnesemia
Gemtuzumab (Mylotarg)—anti-CD33 (IV)	AML	+++	Infusion rx'n, N&V, diarrhea, fever, LFT
Ipilimumab (Yervoy)—binds to cytotoxic T-lymphocyte associated antigen (CTLA-4) (IV)	Melanoma	-	Hepatoxicity, immune-related: enterocolitis, dermatitis, neuropathy, endocrinopathies, ocular disease
Panitumumab (Vectibix)—anti-EGFR (IV)	GI	-	Rash, nail/hair changes, mucositis, diarrhea, hypomagnesemia
Pertuzumab (Perjeta)—anti HER2 (IV)	BR	-	Infusion reactions, cardiomyopathy
Ramucirumab (Cyramza)—anti-VEGFR2 (IV)	GI	+	Thrombosis, bleeding, HTN
Rituximab (Rituxan)—anti-CD20 (IV)	NHL, CLL	+	Infusion rx'n, infections (e.g. JC virus, CMV, PJP), cardiac arrhythmia
Trastuzumab (Herceptin)—anti-Her2 (IV)	BR, GI	-	Infusion rx'n, cardiomyopathy
ZIV aflibercept (Zaltrap)—anti-VEGF (IV)	GI	+	HTN, fatigue, diarrhea, LFT's
Tyrosine kinase inhibitors			
Axitinib (InLyta)—anti-VEGFR (PO)	Renal	-	HTN, thrombosis, bleeding, hypothyroid, LFT, fatigue
Bosutinib (Bosulif)—inhibits BCR-ABL and Src kinases (PO)	CML	++	Diarrhea, nausea, LFT, fluid retention, fever, asthenia, arthralgia, rash
Ceritinib (Zykadia)—targets ALK (PO)	LU	_	Diarrhea, nausea, vomiting, LFT, lung disease, QT prolongation, fatigue
Crizotinib (Xalkori)—inhibits ALK (PO)	LU	++	Interstitial lung disease, LFT, QT prolongation, vision impairment, diarrhea, nausea, vomiting, edema, fatigue
Dasatinib (Sprycel)—BCR-ABL kinase inhibitor (PO)	CML	++	Bleeding, HTN, fluid retention, nausea, vomiting, rash

Antineoplastic Agents (cont'd)

Targeted agents	Activity[a]	Cytopenia	Other major toxicities[b]
Erlotinib (Tarceva)—EGFR inhibitor (PO)	LU, GI	–	Rash, nail/hair changes, mucositis, diarrhea, interstitial lung dx
Gefitinib (Iressa)—EGFR inhibitor (PO)	LU	–	Rash, nail/hair changes, mucositis, diarrhea, interstitial lung dx
Idelalisib (Zydelig)—P13-kinase inhibitor (PO)	CLL, NHL	++	Rash, LFT, hyperglycemia, hypertriglyceremia, pneumonia
Imatinib (Gleevec)—bcr/abl, c-kit inhibitor (PO)	CML, GIST	+	Periorbital edema, nausea, diarrhea, muscle cramps, bowel perforation, fatigue
Lapatinib (Tykerb)—anti-EGFR, HER2 (PO)	BR	++	Dyspnea, diarrhea, nausea, hand-foot, LFT, fatigue
Nilotinib (Tasigna)—BCR-ABL kinase inhibitor (PO)	CML	++	Nausea, constipation, QT prolongation, peripheral edema, rash, myalgia, pancreatitis, LFT bleeding, fatigue
Pazopanib (Votrient)—anti-VEGFR, anti-PDGRF (PO)	Renal, SA	+	LFT, cardiac, proteinuria, hypothyroid, electrolyte abnormalities, hair discoloration, thrombosis, fatigue
Ponatinib (Iclusig)—BCR-ABL kinase inhibitor	CML, ALL	++	CHF, hepatoxicity, pancreatitis, bleeding, fluid retention, neuropathy, thrombosis, HTN, fatigue, electrolyte abnormalities
Regorafenib (Stivarga)—anti-VEGFR, PDGFR (PO)	GI, GIST	++	LFT, bleeding, hand-foot, hypothyroid, HTN, diarrhea, mucositis, fatigue, dysphonia
Sorafenib (Nexavar)—VEGFR inhibitor (PO)	Renal, liver, thyroid	+	Fatigue, diarrhea, acral erythema, nail/hair changes, HTN, bleed, hypothyroidism, hypophosphatemia
Sunitinib (Sutent)—VEGFR inhibitor (PO)	Renal, GIST, PNET	+	Fatigue, diarrhea, acral erythema, nail/hair changes, HTN, bleed, hypothyroidism, hypophosphatemia
Others			
Belinostat (Beleodaq)—histone deacetylase inhibitor (HDAC-I) (IV)	PTCL	_	Nausea, fatigue, anemia, hypokalemia, rash, LFT's
Bortezomib (Velcade)—proteasome inhibitor (IV, SQ)	Myeloma, NHL	++	GI symptoms, fatigue, cytopenia, peripheral neuropathy
Everolimus (Afinitor)—mTOR inhibitor (PO)	CNS, BR, PNET, renal	+	Mucositis, infection, HTN, rash, electrolyte abnormalities, constipation, nausea, vomiting, renal failure, impaired wound healing, edema
Interferon—immune modulatory (IV, SQ)	Melanoma, renal	++	Fatigue, fever, myalgia, LFT, mood changes

Antineoplastic Agents (cont'd)

Targeted agents	Activity[a]	Cytopenia	Other major toxicities[b]
Thalidomide (Thalomid)—anti-angiogenic (PO)	Myeloma	++	Sedation, fatigue, constipation, rash, peripheral neuropathy, thromboembolism
Temsirolimus (Torisel)—mTOR inhibitor (IV)	Renal	+	Rash, mucositis, fatigue, hyperglycemia, hypophosphatemia, hypertriglyceridemia
Vemurafenib (Zelboraf)—BRAF inhibitor (PO)	Melanoma	_	S, QT prolongation, infusion r'xn, LFT's photosensitivity, fatigue, edema
Vismodegib (Erivedge)—hedgehog pathway inhibitor (PO)	Basal cell carcinoma	_	LFT's, fatigue, alopecia, amenorrhea, nausea, vomiting, hyponatremia
Vorinostat (Zolinza)—HDAC-I (PO)	CTCL	-	Diarrhea, nausea, vomiting, fatigue, hyperglycemia, QT prolongation. Thrombosis, alopecia

[a]Abbreviations: *ALK* anaplastic lymphoma kinase, *BR* breast, *chorio* choriocarcinoma, *BMT* bone marrow transplant, *CML* chronic myelogenous leukemia, *CNS* brain tumor, *GI* gastrointestinal, *GIST* gastrointestinal stromal tumor, *GYN* gynecological, *KS* Kaposi sarcoma, *LU* lung, *OV* ovarian, *MM* multiple myeloma, *NHL* non-Hodgkin's lymphoma, *NPC* naso- pharyngeal carcinoma, *PNET* pancreatic neuroendocrine tumor, *RC* renal cell, *S* secondary malignancies, *SA* sarcoma, *T* testicular, *TCL* T-cell lymphoma

[b]Abbreviations: *LFT* elevated liver enzymes/hepatic dysfunction, *muco* mucositis, *photo* photosensitivity

[c]Dose modification may be required for **dose-limiting toxicities** (in **bold**) and also potentially renal and hepatic dysfunction

Oncologic Emergencies

INFUSION REACTIONS

TREAT UNDERLYING CAUSE—stop infusion, **ABC**—$\mathbf{O_2}$ to keep sat >94%, *salbutamol* 2 puffs INH q1h PRN. ***Diphenhydramine*** 50 mg IV×1 dose, ***hydrocortisone*** 100 mg IV×1 dose. **If hypotensive**, give normal saline 500–1000 mL IV bolus and consider *epinephrine* 0.1–0.25 mg slow IV push (1 mg in 10 mL of NS, give 1–2.5 mL). May restart chemotherapy slowly for most drugs. Do not restart if signs/symptoms of anaphylaxis

PROPHYLAXIS (before treatment)—*dexamethasone* 20 mg PO 12 h and 6 h prior and 10 mg IV 30 min prior, *diphenhydramine* 50 mg IV 30 min prior, *ranitidine* 50 mg IV over 10 and 30 min prior, *ephedrine* 30 mg PO 30 min prior. See p. 422 for more details on anaphylaxis

MALIGNANT SPINAL CORD COMPRESSION

PATHOPHYSIOLOGY—tumor invasion of epidural space (usually above L1 level) → surrounds thecal sac → obstruction of epidural venous plexus → vasogenic edema in white and subsequently gray matter → spinal cord infarction; 60% T-spine, 30% L-spine, 10% C-spine. Median survival post-spinal cord compression is 6 months

CAUSES—prostate cancer, breast cancer, lung cancer, renal cell carcinoma, non-Hodgkin's lymphoma, multiple myeloma, cancer of unknown primary, colorectal cancer, sarcoma

CLINICAL FEATURES—**back pain** (particularly may worsen with recumbency, nocturnal), **radicular pain** (band like in abdomen, legs), **weakness** (hip flexion, arm extension), **reflexes** (hyperreflexic, Babinski upgoing), **sensory loss** (usually 1–5 levels down from actual lesion, NO sacral paresthesia), **Lhermitte's sign**, **retention/incontinence** (urinary, bowel), **gait ataxia**

DIAGNOSIS—important to have a high index of suspicion as the diagnosis tends to be delayed until patients have incontinence or difficulty walking. Clinical examination followed by spine imaging (X-ray, CT, MRI). MRI and myelogram are best. Strongly consider imaging of T- and L-spine regardless of clinical findings

TREATMENTS—**corticosteroid** (*dexamethasone* 10 mg IV/PO×1 dose, then 8 mg IV/PO BID. **Treat underlying cause urgently** (radiation ± radical resection, chemotherapy for chemosensitive tumors)

MALIGNANT CAUDA EQUINA SYNDROME

PATHOPHYSIOLOGY—compression of lumbosacral nerves roots (lower motor neurons, mostly below L1 level)

MALIGNANT CAUDA EQUINA SYNDROME (CONT'D)

CLINICAL FEATURES—lower limb weakness, depressed tendon reflexes in legs and sacral paresthesia

DIAGNOSIS—similar to malignant spinal cord compression

TREATMENTS—similar to malignant spinal cord compression

SUPERIOR VENA CAVA SYNDROME

PATHOPHYSIOLOGY—invasion or external compression of the SVC by contiguous pathologic processes involving the right lung, lymph nodes, and other mediastinal structures, or by thrombosis within the SVC. Venous collaterals establish alternative pathways, but despite well-developed collateral drainage patterns, central venous pressures remain high, producing characteristic signs and symptoms of SVC syndrome

CAUSES—**neoplasm** (NSCLC 50%, SCLC, lymphoma, metastatic cancer, germ cell tumor, thymoma, mesothelioma), **inflammatory** (fungal infections, TB, sarcoidosis, sclerosing cholangitis), **thrombosis** (indwelling catheters, pacemaker leads)

CLINICAL FEATURES—dyspnea, facial swelling and head fullness (especially with bending forward), Pemberton's sign (elevation of arms causes facial congestion/cyanosis), arm edema, cough, stridor, cyanosis, plethora, venous distension on face, neck, and chest wall

DIAGNOSIS—CXR, CT chest, bilateral venography. For patients presenting with SVC syndrome and suspected cancer, tissue diagnosis is required (supraclavicular lymph node, sputum cytology, mediastinoscopy, thoracentesis, bronchoscopy)

TREATMENTS—elevate patient's head. **Treat underlying cause** (radiation, chemotherapy for chemosensitive diseases). ***Dexamethasone*** 4 mg PO q6h (for lymphoma and thymoma). Consider **endovascular stenting** if urgent or refractory disease

Related Topics
Febrile Neutropenia (p. 263)
Spinal Cord Compression (p. 253)

HYPERCALCEMIA

PATHOPHYSIOLOGY—local osteolytic hypercalcemia 20% (cytokines), humoral hypercalcemia of malignancy 80% (PTHrP), 1,25$(OH)_2$ vitD-secreting lymphomas, and ectopic hyperparathyroidism (PTH) are all known mechanisms. Median survival of 1 month with hypercalcemia in the advanced cancer setting

CLINICAL FEATURES—bony pain, abdominal pain, constipation, polyuria, renal failure, renal stones, confusion

DIAGNOSIS—Ca, PO_4, albumin, PTH, 1,25$(OH)_2$ vitD, bone scan

SYMPTOM CONTROL—NS 200–500 mL/h IV. Once volume repleted consider furosemide. If malignancy and Ca >3.2 mmol/L [>12.8 mg/dL], **bisphosphonates** (*pamidronate* 60–90 mg in 500 mL NS IV over 2 h, *zoledronate* 4 mg in 50 mL NS IV over 15 min), **steroids** (*prednisone* 60 mg PO daily × 10 days, *hydrocortisone* 200–500 mg IV daily), ***calcitonin*** 200U SC/IM BID

TREAT UNDERLYING CAUSE See HYPERCALCEMIA for more details (p. 402)

NEJM 2005 352:4

TUMOR LYSIS SYNDROME

PATHOPHYSIOLOGY—treatment-induced lysis of tumor cells, leading to release of cell contents → hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia, high LDH → calcium phosphate deposition in renal parenchyma and uric acid nephropathy → oliguria. Usually occurs within 3 days before or 7 days after chemotherapy

RISK FACTORS—underlying renal insufficiency, hyperuricemia, hypovolemia, increased tumor proliferation, high chemosensitivity tumor (aggressive lymphomas, ALL, AML, solid tumors)

DIAGNOSIS—a clinical diagnosis with a combination (but not necessary all) of the following criteria: high uric acid (>475 µmol/L [>4 mg/dL] or ↑ 25% from baseline), high K (>6 mmol/L or ↑ 25% from baseline), high PO_4 (>1.45 mmol/L [>4.5 mg/dL] or ↑ 25% from baseline), low Ca (<1.75 mmol/L [<7 mg/dL] or ↓ 25% from baseline), acute renal failure, arrhythmia, and seizure

TREATMENTS—most important is primary prophylaxis with fluids (NS 150–250 mL/h), *allopurinol* 300 mg PO TID and consider rasburicase (promotes uric acid degradation). Monitor urine output, K, Ca, PO_4, Cr, uric acid, and LDH q6h. Treatment of uric acid nephropathy with aggressive hydration, furosemide diuresis, rasburicase, and dialysis as a last resort

Febrile Neutropenia

See FEBRILE NEUTROPENIA (p. 263)

Chemotherapy-Induced Nausea and Vomiting

NEJM 2008 358:23; JCO 2006 24:18

PATHOPHYSIOLOGY

REFLEX PATHWAY—see p. 123

RISK FACTORS—female, <50 years, previous treatment-related nausea and vomiting, concomitant radiation, and chemotherapy. High alcohol use predicts lower likelihood of chemotherapy-induced nausea and vomiting (CINV)

NCI-CTC GRADING V4.0

Grade	Nausea
1	Loss of appetite without alteration in eating habits
2	Oral intake decreased without significant weight loss, dehydration, or malnutrition
3	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated
4 or 5	Grade not available

Grade	Vomiting
1	1–2 episodes (separated by 5 min) in 24 h
2	3–5 episodes in 24 h
3	≥6 episodes in 24 h; tube feeding, TPN, or hospitalization indicated
4	Life-threatening consequences; urgent intervention required
5	Death

Related Topic
Nausea and Vomiting (p. 123)

EMETOGENIC LEVELS OF INTRAVENOUSLY ADMINISTERED ANTINEOPLASTIC AGENTS

HIGH RISK (>90%)—carmustine >250 mg/m^2, cisplatin, cyclophosphamide >1.5 g/m^2, dacarbazine, mechlorethamine, streptozocin, doxorubicin ≥ 60 mg/m^2, epirubicin >90 mg/m^2, ifosfamide ≥2 g/m^2/dose, doxorubicin and cyclophosphamide, epicrubicin and cyclophosphamide

MODERATE RISK (31–90%)—bendamustine, carboplatin, cyclophosphamide ≥1.5 g/m^2), cytarabine >200 mg/m^2, daunorubicin, doxorubicin <60 mg/m^2, epirubicin ≤90 mg/m^2, idarubicin, ifosfamide <2 g/m^2/dose, irinotecan, methotrexate ≥250 mg/m^2, oxaliplatin, temozolomide

LOW RISK (10–30%)—brentuximzab, cabazitaxel, cytarabine, docetaxel, doxorubicin liposomal, eribulin, etoposide, fluorouracil, gemcitabine, ixabepilone, lapatinib, methotrexate >50 mg/m^2 < 250 mg/m^2, mitomycin, mitoxantrone, paclitaxel, paclitaxel albumin-bound, pemetrexed, topotecan, temsirolimus, trastuzumab, ziv-aflibercept

MINIMAL RISK (<10% risk of CINV in the absence of antiemetic prophylaxis)—bevacizumab, bleomycin, bortezomib, busulfan, cetuximab, cladribine, cytarabine <100 mg/m^2 fludarabine, ipilumumab, methotrexate ≤50 mg/m^2, panitumumab, pertuzumab, rituximab, temsirolimus, trastuzumab, vinblastine, vincristine, vinorelbine

EMETOGENIC LEVELS OF ORALLY ADMINISTERED ANTINEOPLASTIC AGENTS

MEDIUM TO HIGH (>30%)—crizotinib, cyclophosphamide ≥100 mg/m^2/day, etoposide, procarbazine, temozolimide ≥75 mg/m^2/day, vismodegib

MINIMAL TO LOW (≤30%)——capecitabine, dasatinib, erlotinib, everolimus, imatinib, lapatinib, methotrexate, thalidomide, topotecan, vanetinib, vemurafenib, vorinostat

MANAGEMENT

PREVENTION IS KEY

ANTICIPATORY NAUSEA AND VOMITING (–3 to –4 h)—consider use of distraction and benzodiazepines

ACUTE NAUSEA AND VOMITING (0–24 h)—5HT3 antagonists and steroids are key. NK1 antagonists may be added for patients on highly emetogenic chemotherapy

MANAGEMENT (CONT'D)

DELAYED NAUSEA AND VOMITING (>24 h)—associated with cisplatin, cyclophosphamide, ifosfamide at higher doses and doxorubicin. NK1 antagonists, 5HT3 antagonists, and steroids are all effective

CHRONIC NAUSEA AND VOMITING—unlikely to be due to chemotherapy alone. Multi-factorial interventions required. Avoid long-term use of 5HT3/NK1 antagonists

TREATMENT OVERVIEW FOR PREVENTING ACUTE AND DELAYED CINV

Risk	NK1 antagonist[a]	5HT3 antagonist	Steroid	Etc[b]
High[c]	✓	✓	✓	✓
Moderate[c]	(✓)	✓	✓	✓
Low			✓	✓
Minimal				✓

[a]Alternative to NK1 antagonists for highly or moderately emetogenic regimens is olanzapine 10 mg PO Days 1-4, $5HT_3$ antagonist (palonosetron preferred 0.25 mg IV day 1) and steroid day 1

[b]Choices include *metoclopramide* 10 mg PO q4h PRN and *prochlorperazine* 10 mg PO q4h PRN

[c]Highly emetogenic chemotherapy or doxorubicin/cyclophosphamide (AC) combination chemotherapy

TREATMENT ISSUES

HIGH-RISK CHEMOTHERAPY OR AC COMBINATION CHEMOTHERAPY—*aprepitant* 125 mg PO on day 1, then 80 mg PO days 2–3, PLUS *ondansetron* 8–12 mg IV or 16–24 mg PO on day 1, PLUS *dexamethasone* 12 mg PO/IV on day 1, then 8 mg PO days 2–4 PLUS *metoclopramide* 10 mg PO q4h PRN or *prochlorperazine* 10 mg PO q4h PRN

MODERATE-RISK CHEMOTHERAPY—*ondansetron* 8 mg IV or 8 mg PO BID on day 1, then 8 mg PO BID on days 2–3, PLUS *dexamethasone* 12 mg PO/IV on day 1, then 8 mg PO or 4 mg PO BID days 2–3 PLUS *metoclopramide* 10 mg PO q4h PRN or *prochlorperazine* 10 mg PO q4h PRN

LOW-RISK CHEMOTHERAPY—*dexamethasone* 8 mg PO/IV day 1 PLUS *metoclopramide* 10 mg PO q4h PRN or *prochlorperazine* 10 mg PO q4h PRN

LOW, RISK CHEMOTHERAPY—*metoclopramide* 10 mg PO q4h PRN or *prochlorperazine* 10 mg PO q4h PRN

NOTE—for patients with significant nausea and vomiting despite proper oral antiemetic use, consider admission for intravenous hydration and medication administration

Oral Mucositis

PATHOPHYSIOLOGY

RISK FACTORS FOR ORAL MUCOSITIS

- **PERSONAL**—younger age, poor oral hygiene, smoking, alcohol use
- **CHEMOTHERAPY**—bleomycin, capecitabine, chlorambucil, cytarabine, doxorubicin, etoposide, methotrexate, vinblastine, 5-fluorouracil
- **TARGETED AGENTS**—afatinib, cetuximab, erlotinib, everolimus, sorafenib, sunitinib, temsirolimus
- **RADIATION**—head and neck region

COMPLICATIONS OF ORAL MUCOSITIS—severe pain, bleeding, superinfections (bacteremia, febrile neutropenia)

NCI-CTC GRADING V4.0

Grade	Oral mucositis
1	Asymptomatic or mild symptoms; normal diet; intervention not indicated
2	Moderate pain; not interfering with oral intake; modified diet indicated
3	Severe pain; interfering with oral intake
4	Life-threatening consequences; urgent intervention indicated

MANAGEMENT

CRYOTHERAPY—sucking on ice chips during chemotherapy is a reasonable preventative strategy for patients on 5-fluorouracil, edatrexate, or high-dose melphalan (avoid when oxaliplatin is included in regimen)

MANAGEMENT (CONT'D)

ORAL HYGIENE—soft tooth brush, flossing, mouth rinses q4h (0.9% saline, baking soda, or salt and baking soda solution by mixing one teaspoon of baking soda and half teaspoon of salt in 1/L of water), denture care (if applicable)

DOSE ADJUSTMENTS—dose reduction or treatment termination may be considered in severe cases

SUPPORTIVE MEASURES—ensure adequate hydration and monitor nutritional intake. Assess patients for diarrhea as well. Providing optimal pain control is key

- **TOPICAL ANALGESIA**
  - **MAGIC/MIRACLE MOUTHWASH**—generally includes lidocaine for pain control. For a 100 mL solution, mix hydrocortisone 25 mg, glycerin 95% 2 mL, normal saline 52 mL, lidocaine 2% 25 mL, and nystatin 2,083,300 IU or 20.833 mL. Use 10 mL squish and spit q4h–q6h
  - **MORPHINE SULFATE MOUTHWASH**—2 mg/mL in 15 mL of water, swish and spit, q4h to q6h
  - **LIDOCAINE VISCOUS 2%**—10 mL, swish and spit, q4h PRN
- **SYSTEMIC OPIOIDS**—morphine 5 mg IV q4h PRN or 10 mg PO q4h PRN, titrating up as needed
- **INFECTIONS**—**oral candidiasis** (*nystatin* 500,000 IU swish and swallow QID, clotrimazole troches, or fluconazole), **HSV infections** (acyclovir or valacyclovir after cultures taken)

Chemotherapy-Induced Diarrhea

JCO 2004 22:14

PATHOPHYSIOLOGY

RISK FACTORS FOR CHEMOTHERAPY-INDUCED DIARRHEA

- **CHEMOTHERAPY**—carboplatin, capecitabine, cisplatin, cyclophosphamide, cytosine arabinoside, daunorubicin, docetaxel, doxorubicin, 5-fluorouracil, ipilumumab, irinotecan (active metabolite SN 38), lapatinib, oxaliplatin, paclitaxel, methotrexate, topotecan
- **TARGETED AGENTS**—erlotinib, imatinib, sorafenib, sunitinib, vemurafenib

NCI-CTC GRADING V4.0

Grade	Chemotherapy-Induced Diarrhea
1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline
3	Increase of ≥7 stools per day over baseline; incontinence; hospitalization; severe increase in ostomy output compared to baseline; limiting self-care ADL
4	Life-threatening consequences; urgent intervention indicated

MANAGEMENT

DOSE ADJUSTMENTS—dose reduction or treatment termination may be considered in severe cases

FIRST LINE—*loperamide* 4 mg PO, followed by 2 mg every 2 h (or 4 mg every 4 h) until 12 h has elapsed without any diarrhea. May alternate with *diphenoxylate/atropine* (lomotil) 4 mg PO QID

SECOND LINE—*octreotide* 100–150 μg SC every 8 h. Octreotide is a somatostatin analogue that decreases both intestinal transit time and fluid secretion into the small intestine

NOTE—ensure adequate hydration and assess other related symptoms such as oral mucositis, nausea, and vomiting. Remember to stop all laxatives

8

INFECTIOUS DISEASES

Stephanie W. Smith

Fever of Unknown Origin

Infect Dis Clin North Am 2007;21:4
Am J Med Sci 2012;344:4

DIFFERENTIAL DIAGNOSIS

This list is not exclusive, but highlights some important causes of FUO after the common causes of fever have been excluded:

INFECTIONS—**TB** (pulmonary, extrapulmonary, miliary), **abscess** (liver, splenic, perinephric, psoas, diverticular, pelvis), **osteomyelitis**, **endocarditis**, **prosthetic associated infections**

NEOPLASTIC—**hematologic** (lymphoma, leukemia, multiple myeloma, myelodysplastic syndrome), **solid tumors** (renal cell, hepatoma)

COLLAGEN-VASCULAR—**vasculitis** (giant cell arteritis, Still's disease, polyarteritis nodosa, Takayasu's arteritis, granulomatosis with polyangiitis, mixed cryoglobulinemia), **lupus**, **rheumatoid arthritis**

DRUGS—**antimicrobials** (sulfonamides, penicillins, nitrofurantoin, antimalarials), **antihistamines**, **antiepileptics** (barbiturate, phenytoin), **NSAIDs/ASA**, **antihypertensives** (hydralazine, methyldopa), **antiarrhythmics** (quinidine, procainamide), **antithyroid**, **iodides**, **quinine**, **illicit** (cocaine)

UNCOMMON CAUSES OF FUO—**central fever**, **endocrine** (hypothalamic dysfunction, hyperthyroidism, pheochromocytoma, adrenal insufficiency), **infections** (dental abscess, Q fever, leptospirosis, psittacosis, tularemia, melioidosis, syphilis, gonococcemia, chronic meningococcemia, Whipple's disease, yersiniosis, brucellosis), **hereditary periodic fever syndromes** (familial Mediterranean fever, PFAPA syndrome [Periodic Fever with Aphthous Stomatitis and Adenitis], TNFR-1-associated periodic syndrome, hyper-IgD syndrome, Muckle–Wells syndrome, familial cold autoinflammatory syndrome), **alcoholic hepatitis**, **hematoma**, **factitious fever**

PATHOPHYSIOLOGY

DEFINITIONS

- **FEVER OF UNKNOWN ORIGIN** (**FUO**)
  - **FUO**—≥ 38.3 °C [≥101 °F], duration ≥3 weeks, diagnosis uncertain after 3 days in hospital or three outpatient visits
  - **NOSOCOMIAL FUO**—hospitalized patients, ≥38.3 °C [≥101 °F], diagnosis uncertain after 3 days and infection not present or incubating on admission
  - **IMMUNE-DEFICIENT** (**NEUTROPENIC**) **FUO**—> 38.3 °C [≥101 °F], >3 days, neutrophil count ≤500/mm^3. See p. 260 for details
  - **HIV-RELATED FUO**—HIV patients, ≥38.3 °C [≥101 °F], duration ≥3 weeks for outpatients or ≥3 days for inpatients
- **FEVER**, **NYD**—persistent fever that has not yet met the definition for FUO

CLINICAL FEATURES

HISTORY—pattern and duration of fever, associated symptoms (cough, dyspnea, hemoptysis, chest pain, diarrhea, abdominal pain, dysuria, urethral discharge, hematuria, neck stiffness, headache), rash (palpable purpura, exanthem), exposure (food, water, plants, animals, insects, infected human secretions), weight loss, night sweats, travel history, sexual history, HIV risk factors, immunizations, past medical history (rheumatologic disorders, malignancy, alcohol), medications

PHYSICAL—vitals (tachycardia, tachypnea, hypotension, fever, hypoxemia), oral ulcers, lymphadenopathy, nuchal rigidity, respiratory and cardiac examination (murmurs), temporal artery, abdominal examination (hepatosplenomegaly), prostate examination, skin lesions (morphology, distribution), tick bite marks, joint examination

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INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, LDH, CK, serum protein electrophoresis, urinalysis, ESR, CRP, ANA, ENA, RF, C3, C4, ANCA, cryoglobulin
- **MICROBIOLOGY**—blood C&S (including *Mycobacteria*), sputum Gram stain/AFB/C&S, urine C&S, stool C&S, O&P, serology (HBV, HCV, HIV, monospot, CMV IgM, endemic fungi)
- **IMAGING**—CXR, echocardiogram (if suspect endocarditis), CT chest/abd/pelvis as guided by symptoms, FDG-PET (may be useful for identifying sites of inflammation and malignancy in FUO)

SPECIAL

- **ECG**
- **TUBERCULIN SKIN TEST**
- **BIOPSY**—affected tissue (e.g. bone marrow biopsy)

DIAGNOSIS AND PROGNOSTIC ISSUES

DIAGNOSIS—the most important diagnostic strategy is a careful history and physical examination with frequent reassessment

PROGNOSIS—up to 30–50% will not have a diagnosis despite detail workup; 5-year mortality in those without a diagnosis is 3%

MANAGEMENT

EMPIRIC ANTIBIOTICS—ONLY if suspect infectious etiology and therapy cannot be delayed due to severity of patient's disease (see EMPIRIC ANTIBIOTICS p. 289). In general, therapeutic trials of antimicrobials or steroids are discouraged

TREAT UNDERLYING CAUSE

Fever and Rash

DIFFERENTIAL DIAGNOSIS

INFECTIONS

- **GRAM-POSITIVE COCCI**—scarlet fever, toxic shock syndrome, staphylococcal scalded skin syndrome, acute rheumatic fever (erythema marginatum, subcutaneous nodules)
- **GRAM-NEGATIVE COCCI**—meningococcemia (purpura), disseminated gonococcal infection
- **GRAM-NEGATIVE BACILLI**—*Salmonella typhi*, *Pseudomonas* (ecythema gangrenosum), *Vibrio vulnificus*
- **ENDOCARDITIS**
- **SPIROCHETES**—*Borrelia burgdorferi* (Lyme erythema migrans), *Treponema pallidum* (chancre, secondary syphilis)
- **RICKETTSIAL**—Rocky Mountain spotted fever, ehrlichiosis, typhus
- **VIRAL EXANTHEM**—acute HIV, mononucleosis, rubella, measles, roseola, erythema infectiosum, chickenpox, shingles, coxsackie virus, echovirus
- **FUNGAL**—*Blastomyces*, *Coccidioides*, *Histoplasma*

RHEUMATOLOGIC

- **SEROPOSITIVE**—lupus, dermatomyositis
- **SERONEGATIVE**—inflammatory bowel disease, reactive arthritis

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **VASCULITIS**—granulomatosis with polyangiitis, polyarteritis nodosa
- **BEHCET'S DISEASE**

MALIGNANCY—lymphoma, leukemia, metastatic, paraneoplastic

MEDICATIONS—penicillins, cephalosporins, sulfas, barbiturates, phenytoin, procainamide, quinidine

OTHERS—sarcoidosis, erythema nodosum; Sweet's syndrome (acute febrile neutrophilic dermatosis)

CLINICAL FEATURES

SETTINGS

- **AGE**—viral exanthems, scarlet fever, and acute rheumatic fever are more likely in children. Mononucleosis is more common in young adults
- **SEASON**—tick-borne diseases are more common in spring and summer. Coxsackie virus and echovirus are more common in summer and fall. Meningococcus and parvovirus are more common in winter and spring
- **GEOGRAPHIC LOCATION**—Lyme disease in Pacific northwest, the Midwest, and the northeast USA and some southern Canadian locations. RMSF in south-central and Atlantic

CLINICAL FEATURES (CONT'D)

states. Ehrlichiosis in midwestern, south-central, and southeastern states. Tularemia in western, southeastern, and south-central states and Canada. Relapsing fever (*Borrelia hermsii*) in mountainous areas of the western USA. Endemic fungal infections include *Blastomyces dermatitidis* (southeastern states, Manitoba, and Ontario), *Coccidioides immitis* (southwestern states), and *Histoplasma capsulatum* (Mississippi, Ohio River valleys, and Quebec)

HISTORY—pattern and duration of fever, associated symptoms (cough, dyspnea, chest pain, diarrhea, abdominal pain, dysuria, urethral discharge, neck stiffness, headache), rash (prodrome, location, progression, treatment), exposure (food, water, plants, animals, infected human secretions), weight loss, night sweats, travel history, sexual history, immunizations, past medical history (rheumatologic disorders, malignancy), medications

PHYSICAL—vitals (tachycardia, tachypnea, hypotension, fever, hypoxemia), oral ulcers, lymphadenopathy, nuchal rigidity, respiratory and cardiac examination (murmurs), abdominal examination (hepatosplenomegaly), skin lesions (morphology, distribution), tick bite eschar, joint examination

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, ESR, urinalysis
- **MICROBIOLOGY**—blood C&S, sputum Gram stain/AFB/C&S, urine C&S, monospot test, CMV IgM, EBV, HIV, and other serologies (e.g. rickesttsial serology)

SPECIAL

- **LUMBAR PUNCTURE**—if suspect meningococcus
- **SKIN BIOPSY**—dermatology consult
- **INFLAMMATORY WORKUP**—CRP, ANA, ENA

MANAGEMENT

ISOLATION PRECAUTIONS—droplet/airborne plus contact precautions for uncertain diagnosis; for purpura with bacterial sepsis, institute droplet and contact isolation precautions. See p. 304 for more details

TREAT UNDERLYING CAUSE

SPECIFIC ENTITIES

RICKETTSIAL INFECTIONS (WITHIN NORTH AMERICA)

- **THEMES**—all transmitted by ticks, except Q fever (*Coxiella burnetii*). All associated with a rash, myalgias, and headache, except Q fever and ehrlichiosis. All involve some degree of vasculitis and DIC as part of pathogenesis. All can be treated with doxycycline
- **ROCKY MOUNTAIN SPOTTED FEVER**—*Rickettsia rickettsii* transmitted by ticks. Most common in mid-Atlantic states. Macular/maculopapular rash begins on extremities and moves centrally, involves palms/soles. Treat with doxycycline
- **MURINE TYPHUS**—flea vector. Rash begins centrally and moves peripherally. Treat with doxycycline or chloramphenicol
- **EHRLICHIA**—*E. chaffeensis* (human monocytic ehrlichiosis) transmitted by lone star tick. Peaks in May to July. Infects lymphocytes, monocytes, and neutrophils intracellularly. Fever, headache, myalgia, leukopenia, thrombocytopenia, and elevated transaminases; maculopapular or petechial rash in 1/3. Human granulocytic anaplasmosis is caused by a related *Ehrlichia* and produces similar illness without rash. Transmitted by Ixodes tick and co-infection with Lyme disease possible. Treat with doxycycline
- **Q FEVER**—*Coxiella burnetii* transmitted by respiratory spread from infected animal body fluids (e.g. cattle, sheep, goats, cats). No rash. Fever, pneumonitis, hepatitis, endocarditis, CNS symptoms. Treat with doxycycline

LYME DISEASE

- **PATHOPHYSIOLOGY**—*Borrelia burgdorferi* transmitted by tick bite after attachment for >24 h; think about concomitant tick borne diseases
- **CLINICAL FEATURES**—most common tick-borne disease in USA, particularly coastal Atlantic States and California during spring and summer
  - **STAGE 1 (EARLY)**—first 3–30 days, erythema migrans, fever, meningismus, lymphadenopathy
  - **STAGE 2 (DISSEMINATED)**—weeks to months, hematogenous spread with **neurological symptoms** (facial nerve palsy, lymphocytic meningitis, encephalitis, chorea, myelitis, radiculitis, peripheral neuropathy) and **carditis** (AV block, dilated cardiomyopathy); may have multiple skin lesions of erythema migrans

SPECIFIC ENTITIES (CONT'D)

- **STAGE 3 (LATE)**—months to years, mono- or oligoarthritis, acrodermatitis chronica atrophicans (in Europe), progressive encephalitis, dementia. Not amenable to antibiotic therapy
- May develop post-Lyme syndrome with musculoskeletal pain, neurocognitive symptoms, dysesthesias and fatigue (not amenable to antibiotic therapy)

- **DIAGNOSIS**—seology (anti-B. burgdorferi ELISA). If positive, confirm with Western blot
- **PREVENTION**—protective clothing and tick repellants. After tick bite (>36 h in hyperendemic area), consider *doxycycline* 200 mg × 1 dose within 72 h of the tick bite
- **TREATMENTS**—**stage 1** (*doxycycline* 100 mg PO BID × 10–21 days, or *cefuroxime* 500 mg PO BID × 10–21 days). **Lyme carditis** (*ceftriaxone* 2 g IV × 14–21 days if third degree AV block; otherwise, same as stage I with oral antibiotics). **Neurologic Lyme** (*ceftriaxone* 2 g IV × 14–21 days). **Lyme arthritis** (*doxycycline* 100 mg BID × 28 days, amoxicillin)
- **JARISCH–HERXHEIMER REACTION**—up to 15% of patients may experience transient worsening of symptoms during first 24 h of treatment. This results from the host immune response to antigen release from dying organisms (typically Lyme and syphilis) causing fever, chills, myalgias, and exacerbation of rash

BABESIOSIS (malaria like; does not cause rash)

- **PATHOPHYSIOLOGY**—*B. microti* (USA) or *B. divergens* (Europe) transmitted by Ixodes ticks (which also transmit Lyme disease and *Ehrlichia*) → fever, chills, sweats, malaise, myalgias, arthralgias, headache 5–33 days after, particularly in immunosuppressed individuals
- **CLINICAL FEATURES**—endemic in southern New England, southern New York, Wisconsin, and Minnesota
- **DIAGNOSIS**—blood smear ('Maltese cross' formations, not seen in malaria), PCR, serology
- **TREATMENTS**—atovaquone plus azithromycin

SPECIFIC ENTITIES (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE ERYTHEMA MIGRANS?

	Sens (%)
History (US studies)	
Systemic symptoms	65
Fatigue	47
Headache	36
Myalgias	35
Arthralgias	35
Fever	33
Pruritus	33
Stiff neck	31
History of a tick bite	26
Dysesthesia	20
Nausea and vomiting	11
Physical (US studies)	
Solitary lesion	81
Lymphadenopathy	22
Multiple lesions	21
Central clearing of rash	19

APPROACH—"no single component of the history or physical examination emerges as one that makes the diagnosis of erythema migrans highly likely. These signs and symptoms have not been examined in combination. Laboratory testing has limited utility. In endemic areas, the combination of history of a tick bite, a solitary lesion of appropriate size, morphology and presence of systemic symptoms is consistent with erythema migrans. In non-endemic areas, these same factors are also suggestive of this diagnosis and should prompt further investigation"

JAMA 2007 297:23

Related Topic
Exanthematous Lesions (p. 413)

Fever and Joint Pain

See JOINT PAIN AND FEVER (p. 312)

Sepsis

See SEPSIS (p. 108)

Febrile Neutropenia — IDSA Guidelines 2011

DIFFERENTIAL DIAGNOSIS

BACTERIAL

- **GRAM POSITIVE**—*S. aureus*, coagulase-negative staphylococci, *Streptococcus pneumoniae*, corynebacterium
- **GRAM NEGATIVE**—*Enterobacter*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas*, *C. difficile*, anaerobes
- **TB**

VIRAL—HSV, VZV, CMV, EBV, HHV6, enterovirus, RSV, influenza and other respiratory viruses

FUNGAL—*Candida, Aspergillus*, *Cryptococcus*, *Fusarium*

REACTIVATION OF LATENT INFECTION—*Histoplasma*, *Coccidioides*, *Toxoplasma*, tuberculosis

PATHOPHYSIOLOGY

DEFINITION—single temp ≥38.3 °C [101 °F] or ≥38 °C [100.4 °F] for >1 h, ANC $<0.5\times10^9$/L or $<1.0\times10^9$/L + expected nadir $<0.5\times10^9$/L

ABSOLUTE NEUTROPHIL COUNT (ANC)—neutrophils + bands

PATHOGENESIS—chemotherapy-induced injury to mucosal barriers, immune defects due to drugs or underlying disease and invasive devices. With the attenuated immune response, patients may be relatively asymptomatic until they decompensate due to overwhelming infection. Fever is sometimes the only warning sign and should always be taken seriously in patients at risk of developing neutropenia

NEUTROPENIA-ASSOCIATED FEBRILE EPISODES—most commonly idiopathic; bacterial source identified in approximately 30% of episodes, usually from patient's own endogenous flora. Fungal infections replace bacterial infections in prominence after 7 days. Fever usually abates with return of neutrophils. If fever persists or returns after neutropenia resolves, consider hepatosplenic candidiasis

CLINICAL FEATURES

HISTORY—patients usually asymptomatic other than fever. Determine severity and duration of fever, associated signs and symptoms (cough, dyspnea, chest pain, diarrhea, abdominal pain, dysuria, urethral discharge, neck stiffness, headache, rash), recent chemotherapy (nadir of neutrophil counts usually 10–14 days post-treatment), weight loss, night sweats, travel history, sexual history, immunizations, past medical history (malignancy, rheumatologic disorders), medications (chemotherapy, GCSF)

PHYSICAL—vitals (tachycardia, tachypnea, hypotension, fever, hypoxemia), oral ulcers, lymphadenopathy, nuchal rigidity, respiratory and cardiac examination (murmurs), abdominal examination (hepatosplenomegaly), skin lesions (morphology, distribution). Important sites to examine include venous access devices, sinuses, and perianal region for abscess. Digital rectal examination is not recommended as potential rectal tear and translocation of gut microbes (also avoid rectal thermometers, enemas, suppositories)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, urinalysis
- **MICROBIOLOGY**—blood C&S × 2 (culture peripheral blood in addition to central line ports), sputum Gram stain/AFB/C&S, urine C&S, stool C&S, O&P, *C. difficile* toxin (if diarrhea)
- **IMAGING**—CXR

SPECIAL

- **SINUS X-ray**

MANAGEMENT

LOW RISK (ANC $>0.1\times10^9$/L, peak temperature <39 °C [102.2 °F], no significant symptoms or signs, no significant comorbidities, nearly normal renal and hepatic function, neutropenia ≤7 days, no dehydration, no hypotension, age <60 years)—*ciprofloxacin* 500 mg PO BID + *amoxicillin–clavulanate* 500 mg PO q8h. May send home with follow-up

HIGH RISK (anticipated prolonged >7 days duration and profound neutropenia [ANC $\leq0.1\times10^9$/mL] and/or significant medical comorbid conditions such as hypotension, pneumonia, new-onset abdominal pain, or neurologic changes)—admit for intravenous antibiotics

- **FIRST LINE**—one of *imipenem* 500 mg IV q6h, *meropenem* 2 g IV q8h, *ceftazidime* 2 g IV q8h, *cefepime* 2 g IV q8h, *piperacillin/tazobactam* 4.5 g IV q8h, *piperacillin* 3 g IV q4h plus *tobramycin* 2–2.5 mg/kg IV q8h, *clindamycin* 600 mg

MANAGEMENT (CONT'D)

IV q8h plus *tobramycin* 7 mg/kg IV q24h, or *piperacillin/tazobactam* 4.5 g IV q8h plus *gentamicin* 2–2.5 mg/kg IV q8h

- **SECOND LINE**—add ***vancomycin*** 1 g IV q12h if suspect line infection, known colonization MRSA, Gram-positive blood culture, or hypotension
- **THIRD LINE**—add **antifungal** if febrile after 4–7 days and hemodynamically unstable (*fluconazole* 400 mg IV daily, *itraconazole* 200 mg IV daily, *amphotericin B* 0.5–1 mg/kg IV daily over 4 h, *caspofungin* 70 mg on first day followed by 50 mg IV daily)
- Unexplained persistent fever in a patient whose condition is otherwise stable rarely requires an empirical change to the initial antibiotic regimen. If an infection is identified, antibiotics should be adjusted accordingly

GCSF SUPPORT—see TREATMENT ISSUES below

CATHETER REMOVAL—necessary for most patients with bacteremia/candidemia with organisms other than coagulase-negative *Staphylococci*

TREATMENT ISSUES

MODIFICATION OF THERAPY DURING FIRST WEEK OF TREATMENT

- **IF PATIENT BECOMES AFEBRILE IN 3–5 DAYS**
  - **KNOWN ORGANISM**—switch to specific antibiotics
  - **UNKNOWN ETIOLOGY AND LOW RISK**—switch to ciprofloxacin plus amoxicillin–clavulanate after afebrile for 48 h
  - **UNKNOWN ETIOLOGY AND HIGH RISK**—continue same antibiotics
- **IF PERSISTENT FEVER DURING FIRST 3–5 DAYS**
  - **CLINICALLY STABLE BY DAY 3**—continue antibiotics, stop vancomycin if cultures negative
  - **PROGRESSIVE DISEASE BY DAY 3**—change antibiotics
  - **FEBRILE AFTER DAY 5**—add antifungal

DURATION OF ANTIBIOTIC TREATMENT

- **IF AFEBRILE BY DAY 3**
  - **STOP ANTIBIOTICS**—if (1) ANC $\geq 0.5 \times 10^9$/L for 2 consecutive days, afebrile for ≥48 h, cultures negative, and no obvious signs of infection, or if (2) ANC $< 0.5 \times 10^9$/L by day 7, but afebrile for 5–7 days, patient initially at low risk, and no subsequent complications
  - **CONTINUE ANTIBIOTICS**—if above criteria not met

TREATMENT ISSUES (CONT'D)

- **IF PERSISTENT FEVER ON DAY 3**
  - **STOP ANTIBIOTICS**—if ANC $\geq 0.5 \times 10^9$/L for 4–5 consecutive days
  - **CONTINUE ANTIBIOTICS**—if ANC $< 0.5 \times 10^9$/L, reassess and continue antibiotics for 2 weeks. Consider stopping therapy if no disease site is found and condition is stable

PRE-MEDICATIONS FOR AMPHOTERICIN B—*meperidine* 50 mg IV, *acetaminophen* 2 tabs PO, *hydrocortisone* 25 mg IV 30 min before dose, and repeat × 1 1–2 h after administration

ASCO 2006 GUIDELINE FOR GCSF USE

- **PRIMARY PROPHYLAXIS**—GCSF is recommended for the prevention of febrile neutropenia if
  - **HIGH-RISK PATIENTS**—based on age (>65), medical history (poor performance status, previous febrile neutropenia, extensive prior treatment, poor nutrition, open wounds, active infections), disease characteristics (bone marrow involvement), and myelotoxicity of the chemotherapy regimen (chemoradiation)
  - **CHEMOTHERAPY REGIMENS**—20% or higher risk of febrile neutropenia or dose dense regimens
- **SECONDARY PROPHYLAXIS**—GCSF is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (in which primary prophylaxis was not received), in which a reduced dose may compromise disease-free survival overall survival, or treatment outcome
- **TREATMENT OF PATIENTS WITH FEBRILE NEUTROPENIA**—GCSF should be given to those with high risk of developing complications, including expected prolonged (>10 days) and profound ($< 0.1 \times 10^9$/L) neutropenia, age >65 years, uncontrolled primary disease, pneumonia, hypotension and multi-organ dysfunction (sepsis), invasive fungal infection, being hospitalized at the time of the development of fever
- **SPECIAL SITUATIONS**
  - **STEM CELL TRANSPLANT**—to mobilize peripheral blood progenitor cell often in conjunction with chemotherapy. Also administered after autologous, but not allogeneic stem cell transplantation
  - **DLBCL**—prophylactic GCSF should be given for patients with diffuse aggressive lymphoma age 65 and older treated with

TREATMENT ISSUES (CONT'D)

curative chemotherapy (CHOP or more aggressive regimens)

- **AML**—may be given shortly after completion of the initial induction chemotherapy to modestly decrease the duration of neutropenia
- **ALL**—recommended after the completion of the initial first few days of chemotherapy of the initial induction or first post-remission course, thus shortening the duration of neutropenia by approximately 1 week
- **MDS**—may be used to increase the ANC in neutropenic patients. Intermittent administration of CSFs may be considered in a subset of patients with severe neutropenia and recurrent infections
- **POST-RADIATION**—GCSF should be given to patients exposed to lethal doses of total body radiotherapy, but not doses high enough to lead to certain death due to injury to other organs

J Clin Oncol 2006 24:19

SPECIFIC ENTITIES

NECROTIZING ENTEROCOLITIS (typhlitis)

- **PATHOPHYSIOLOGY**—mucosal injury in patients with profound neutropenia → impaired host defense → necrosis of bowel wall, involving cecum extending into ascending colon and terminal ileum
- **CLINICAL FEATURES**—abdominal pain (especially RLQ) in neutropenic patients
- **DIAGNOSIS**—CT abd. Avoid barium enema and colonoscopy
- **TREATMENTS**—bowel rest, NG suction, IV fluids, nutritional support, broad spectrum antibiotics, GCSF. Surgical indications include peritonitis, perforation, persistent GI bleeding, or clinical deterioration

Related Topics
Chemotherapy (p. 246)
Neutropenia (p. 164)
Sepsis (p. 108)
Stem Cell Transplant (p. 201)

Fever with Travel History

NEJM 2002 347:7
http://www.cdc.gov
Clin Infect Dis 2007 44:12

DIFFERENTIAL DIAGNOSIS

FEVER WITH CNS INVOLVEMENT

- **BACTERIAL**—meningococcal, typhoid fever, rickettsial, leptospirosis
- **MYCOBACTERIAL**—tuberculosis
- **VIRAL**—Japanese encephalitis, West Nile encephalitis, tick-borne encephalitis, poliomyelitis, rabies
- **FUNGAL**—coccidioidomycosis
- **PARASITIC**—malaria, angiostrongyliasis, trypanosomiasis

FEVER WITH RESPIRATORY INVOLVEMENT

- **BACTERIAL**—*S. pneumoniae*, mycoplasma, Legionella, Q fever, typhoid fever, scrub typhus
- **MYCOBACTERIAL**—tuberculosis
- **VIRAL**—influenza, parainfluenza, metapneumovirus, respiratory syncytial virus, adenovirus, dengue, coronavirus
- **FUNGAL**—histoplasmosis, coccidioidomycosis
- **PARASITIC**—malaria, Loeffler's syndrome (migration of larval helminths such as ascaris, strongyloides, and hookworm)

DIFFERENTIAL DIAGNOSIS (CONT'D)

FEVER WITH RASH—see FEVER AND RASH (p. 260)

HEMORRHAGIC FEVER

- **BACTERIAL**—rickettsial, meningococcemia, leptospirosis
- **VIRAL**—dengue, yellow fever, Ebola fever, Lassa fever, Marburg
- **PARASITIC**—malaria

FEVER WITH SEXUAL OR BLOOD EXPOSURES—syphilis, CMV, EBV, HIV, HBV

FEVER WITH EOSINOPHILIA—parasitic (acute hookworm, ascaris, strongyloides, acute schistosomiasis, visceral larva migrans, lymphatic filariasis, acute trichinosis)

FEVER WITH THROMBOCYTOPENIA—malaria, typhoid fever, dengue shock syndrome, ehrlichiosis, Rocky Mountain spotted fever

ACUTE TRAVELER'S DIARRHEA ± FEVER

- **BACTERIAL**—Enterotoxigenic or enteroaggregative *E. coli*, *Campylobacter jejuni*, *Salmonella*, *Shigella*, *Vibrio*, *Aeromonas*, *Plesiomonas*, *C. difficile*

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **VIRAL**—Caliciviruses (Norwalk, Norwalk-like), rotaviruses, Ebola fever, enteroviruses
- **PARASITIC**—*Giardia lamblia*, *Cryptosporidium parvum*, *Entamoeba histolytica*, *Cyclospora cayetanensis*, *Isospora belli*, *E. polecki*, *Balantidium coli*, *Trichinella spiralis*

CHRONIC TRAVELER'S DIARRHEA ± FEVER

- **BACTERIAL**—Enteroaggregative or enteropathogenic *E. coli*, *C. jejuni*, *Shigella*, *Salmonella*, *Yersinia enterocolitica*, *Aeromonas*, *Plesiomonas*, *C. difficile*, *Tropheryma whippelii*
- **MYCOBACTERIAL**—tuberculosis, *M. avium* complex
- **FUNGAL**—*Paracoccidioides brasiliensis*, *Histoplasma capsulatum*
- **PARASITIC**—*G. lamblia*, *E. histolytica*, *Cryptosporidium parvum*, *C. cayetanensis*, *Trichuris trichiura*, *Strongyloides stercoralis*, Schistosomiasis, *Capillaria philippinensis*, *Fasciolopsis buski*, *Metagonimus yokogawai*, Echinostoma
- **NON-INFECTIOUS**—small-bowel overgrowth syndrome, disaccharidase deficiency, tropical sprue, irritable bowel syndrome, inflammatory bowel disease, cancer, laxative use, endocrinopathy, dysmotility, idiopathic

www.phac-aspc.gc.ca/publicat/ccdr-rmtc/06vol32/acs-01/index-eng.php

CLINICAL FEATURES

HISTORY—pattern and duration of fever, associated symptoms (cough, dyspnea, chest pain, diarrhea, abdominal pain, dysuria, urethral discharge, neck stiffness, headache), weight loss, night sweats, travel history (specific itinerary, activities and exposures including food and fresh/saltwater history, incubation period), sexual history, immunization status, antimalarial chemoprophylaxis (medications, degree of adherence), past medical history (rheumatologic disorders, malignancy), medications

PHYSICAL—vitals (tachycardia, tachypnea, hypotension, fever, hypoxemia), oral ulcers, lymphadenopathy, nuchal rigidity, respiratory and cardiac examination (murmurs), abdominal examination (hepatosplenomegaly), skin lesions (morphology, distribution), tick bite marks, joint examination

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, urinalysis
- **MICROBIOLOGY**—blood C&S, sputum Gram stain/AFB/C&S, urine C&S, stool C&S, O&P, C. diff toxin A/B, malaria thick and thin smear (repeat × 1 within 12–24 h if initially negative result), serologies (HIV, dengue, rickettsiae, schistosomiasis, strongyloidiasis, leptospira, HAV, HBV, HCV, Hepatitis E)
- **IMAGING**—CXR, US abd guided by symptoms

SPECIAL

- **LUMBAR PUNCTURE**

PRE-TRAVEL CONSIDERATIONS

VACCINATIONS—standard regardless of travel (influenza, pneumococcal if age >65, hepatitis B, MMR, DPT), developing countries (hepatitis A), specific countries (meningococcal, Japanese encephalitis, yellow fever), high-risk activity (rabies), outbreaks (cholera)

MALARIA PROPHYLAXIS—see below

DIARRHEA PROPHYLAXIS—ciprofloxacin and imodium if diarrhea develops

SPECIFIC ENTITIES

PRIORITY—focus on those illnesses that are potentially fatal or may be public health threats

TOP TRAVEL-RELATED INFECTIONS—malaria, typhoid fever, dengue fever, diarrheal disease, respiratory infections, Lyme disease, Q fever, brucellosis

MALARIA—the most important cause of fever in returning travelers. *P. falciparum* can be rapidly fatal and must be ruled out in all febrile travelers returning from malaria-endemic regions. It has the shortest incubation period and >90% of affected travelers will become ill within 30 days of return

- **PATHOPHYSIOLOGY**—anopheline mosquito bite transmits sporozoites → travel to liver and invade hepatocytes → divide and form schizonts which contain merozoites (asymptomatic) → rupture after 6–16 days and release merozoites into the bloodstream → infect erythrocytes and mature from ring forms to trophozoites to mature schizonts (asexual form) over 48 (*P. vivax*, *P. ovale*, *P. falciparum*) or 72 (*P. malariae*) hours → merozoites released from erythrocytes (fever, anemia, lactic acidosis, cytokine release) and infect new red cells → few merozoites differentiate into male or female gametocytes (sexual forms) can circulate in blood until ingested by mosquito. *P. vivax* and *P. ovale* may stay dormant in the liver as hypnozoites and may cause late relapse by reactivating after many months. In contrast, *P. falciparum* and *P. malariae* have no liver stage and do not

SPECIFIC ENTITIES (CONT'D)

cause relapse. *P. falciparum* specifically can induce obstruction of microvascular blood flow, and may lead to organ dysfunction (e.g. cerebral malaria, renal failure, ARDS, hypoglycemia, anemia, DIC, and gastroenteritis)

- **CLINICAL FEATURES**—*P. falciparum* is acquired mostly from sub-Saharan Africa, while *P. vivax* is mostly from Asia or Latin America. Symptoms include spiking fevers, chills, headache, back pain, cough, GI problems. Splenomegaly and thrombocytopenia without leukocytosis may be present. Cerebral malaria (*P. falciparum*) presents as altered level of consciousness or seizures and is universally fatal if untreated
- **DIAGNOSIS**—thick and thin smear (need to repeat over 48 h to rule out malaria)
- **PROPHYLAXIS**—the relative risk of contracting malaria varies by geographic region: Caribbean 4, North Africa 7, South America 8, Southeast Asia 12, Central America 38, South Asia 54, Oceania 77, and sub-Saharan Africa 208. Travelers should be advised to wear long sleeves/pants between dusk and dawn, use mosquito repellents containing 30–50% DEET, and consider permethrin-treated mosquito nets. Chloroquine may be used for travel to destinations with chloroquine-sensitive *P. falciparum* (e.g. most of Central America and parts of the Middle East). For destinations where chloroquine-resistant *P. falciparum* is present, chemoprophylaxis with atovaquone–proguanil, mefloquine, or doxycycline should be used. Give atovaquone–proguanil or doxycycline for travel to destinations with *P. falciparum* resistance to chloroquine, mefloquine, and sulfonamides (e.g. regions of Thailand, Cambodia, China, Laos, and Vietnam). Atavaquone–proguanil associated with fewest side effects. Mefloquine has ease of weekly dosing. Doxycycline is the cheapest, but requires prolonged course and causes sun sensitization. CDC 2010 risk assessment and prophylaxis recommendations are available online at
  http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/malaria-risk-information-and-prophylaxis.aspx
- **TREATMENTS**—artesunate has emerged as the treatment of choice for complicated malaria. Other options include quinine–doxycycline, atovaquone–proguanil, and mefloquine. Chloroquine–primaquine for non-falciparum

NEJM 2008 359:6
www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/35s1/index-eng.php

SPECIFIC ENTITIES (CONT'D)

TYPHOID FEVER

- **PATHOPHYSIOLOGY**—acquired after exposure to food or water contaminated by *Salmonella typhi*
- **CLINICAL FEATURES**—mainly in developing countries. Fever, chills, headache, myalgia, abdominal pain and constipation (uncommonly diarrhea), relative bradycardia, splenomegaly, and rose spots (faint salmon-colored macules on the abdomen and trunk). Septic symptoms from intestinal perforation may occur in second week
- **DIAGNOSIS**—blood, stool, urine, or bone marrow (highest sensitivity) culture; CBC may show leukopenia
- **TREATMENTS**—fluoroquinolones, ceftriaxone, azithromycin

DENGUE FEVER (break-bone fever)

- **PATHOPHYSIOLOGY**—flavivirus transmitted by mosquito → flu-like illness 4–7 days later → may develop lymphadenopathy, maculopapular/petechial rash → dengue shock syndrome and dengue hemorrhagic fever if previously exposed to other serotypes
- **CLINICAL FEATURES**—acquired mostly from tropical and subtropical areas. Fever, headache, retro-orbital pain, severe myalgia/arthralgia. Leukopenia and thrombocytopenia
- **DIAGNOSIS**—serology
- **TREATMENTS**—supportive

EBOLA FEVER

- **EPIDEMIOLOGY**—flavivirus possibly transmitted by fruit bats → person to person transmission occurs from direct contact with blood or bodily fluids (saliva, blood, vomit, stool or semen) of infected symptomatic patients. Incubation period is 2–21 days. 2014 outbreaks in Sierra Leon, Guinea, and Liberia
- **CLINICAL FEATURES**—early symptoms include fever, headache, myalgia/arthralgia, vomiting, diarrhea, abdominal pain, conjunctival injection, and rash. Late symptoms include bleeding, shock, delirium and death
- **DIAGNOSIS**—high index of suspicion if patient has recently been in endemic area during an Ebola outbreak. Serology (sens 91%) and RT-PCR (sens close to 100%, spc 97%)
- **TREATMENTS**—rapid isolation. Supportive measures are the mainstay. An experimental therapy, ZMapp, consists of 3 monoclonal antibodies against Ebola viral antigens. Its efficacy has not been proven

CHIKUNGUNYA FEVER

- **PATHOPHYSIOLOGY**—mosquito-borne viral infection acquired in Africa and Asia. Large outbreaks ongoing in Indian Ocean islands and India

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—fever (usually within 2–4 days of exposure) with severe joint pains involving small joints of hands, wrists, and ankles; may be prolonged. Leukopenia, thrombocytopenia, and elevated transaminases may be seen
- **DIAGNOSIS**—serology (acute and convalescent)
- **TREATMENTS**—symptomatic with NSAIDs

RICKETTSIAL INFECTIONS (OUTSIDE OF NORTH AMERICA)

- **PATHOPHYSIOLOGY**—African tick typhus (*Rickettsia africae*), Mediterranean tick typhus (*R. conorii*), and scrub typhus (*Orientia tsutsugamushi*) are all transmitted by ticks
- **CLINICAL FEATURES**—tick bite ± inoculation eschar with a triad of fever, headache, and myalgia. Rash may be present. Lymphadenopathy, leukopenia, and thrombocytopenia
- **DIAGNOSIS**—serology
- **TREATMENTS**—doxycycline

RICKETTSIAL INFECTIONS (WITHIN OF NORTH AMERICA)—SEE FEVER AND RASH (p. 260) **LEPTOSPIROSIS**

- **PATHOPHYSIOLOGY**—*Leptospira interrogans*, zoonosis more common in tropical areas
- **CLINICAL FEATURES**—history of exposure to freshwater. Fever, headache, myalgia, rash, conjunctival suffusion. May be associated with aseptic meningitis, uveitis, elevated transaminases, jaundice, proteinuria, and microscopic hematuria; fulminant syndrome with jaundice, renal failure, and hemorrhage (Weil's disease)
- **DIAGNOSIS**—serology; culture of blood, urine, and CSF
- **TREATMENTS**—doxycycline or amoxicillin for mild disease; penicillin/ampicillin or ceftriaxone/cefotaxime IV for severe disease

BRUCELLOSIS (undulant fever, Mediterranean fever)

- **PATHOPHYSIOLOGY**—Gram-negative facultative intracellular coccobacilli
- **CLINICAL FEATURES**—transmitted by drinking or eating infected animal products (milk), inhalation, or direct animal contact through skin

SPECIFIC ENTITIES (CONT'D)

wounds. Other than fever, may involve any organ system, particularly joints (sacroiliitis), GU (epididymo-orchitis), CNS (meningitis), eyes (uveitis), cardiac (endocarditis), pulmonary (pneumonitis, pleural effusion, empyema), and can cause abscesses (hepatic, splenic, thyroid, epidural). May develop into chronic hepatosplenic disease

- **DIAGNOSIS**—blood cultures, serology
- **TREATMENTS**—doxycycline plus streptomycin or rifampin

NEJM 2007 356:8

SCHISTOSOMIASIS

- **PATHOPHYSIOLOGY**—trematode worms *S. haematobium*, *S. mansoni*, *S. intercalatum* in sub-Saharan Africa, *S. mansoni* in part of South America, *S. japonicum* in Asia, *S. mekongi* in Cambodia. Freshwater exposure → cercariae penetrate skin → larvae migrate to lung through venous circulation → migrate to heart → migrate to liver, where they mature and pair off → migrate to mesenteric venules of bowel (*S. mansoni*, *mekongi*, *japonicum*, *and intercalatum*) bladder (*S. hematobium*), where females lay eggs → excreted into feces or urine → mature to cercariae
- **CLINICAL FEATURES**—this parasitic infection is generally seen in patients from endemic areas instead of travelers. Initial penetration of skin may cause pruritus. Acute schistosomiasis (Katayama fever) includes fever, headache, myalgias, RUQ pain, bloody diarrhea, and dyspnea. Chronic schistosomiasis with granuloma formation is due to host's immune response to schistosome eggs, leading to hepatic (cirrhosis), intestinal (diarrhea, occult blood, fibrosis) or genitourinary tract symptoms (hematuria, dysuria, calcification, fibrosis), and rarely CNS (seizures, focal deficit, transverse myelitis) involvement
- **DIAGNOSIS**—serology, schistosome eggs in feces or urine, biopsy of rectum or bladder
- **TREATMENTS**—*praziquantel* 20 mg/kg PO q8h × 2 doses (3 doses for *S. japonicum* and *mekongi*); adjunctive corticosteroids for Katyama fever

Pneumonia

See PNEUMONIA (p. 7)

Endocarditis

See ENDOCARDITIS (p. 60)

Meningitis

NEJM 2006 354:1

DIFFERENTIAL DIAGNOSIS FOR FEVER AND NEUROLOGICAL SYMPTOMS

★DIMS★

DRUGS—neuroleptic malignant syndrome, serotonin syndrome, sympathomimetics, alcohol withdrawal

INFECTIOUS

- **MENINGITIS**—bacterial (*S. pneumoniae*, *N. meningitidis*, *H. influenzae*, *L. monocytogenes*, *Klebsiella*, *E. coli*, *Serratia*, *Pseudomonas*), viral (enterovirus, VZV, influenza, mumps, HIV), TB, fungal (*Cryptococcus*)
- **ENCEPHALITIS**—HSV, West Nile, St. Louis, Equine, La Crosse
- **ABSCESS**—bacterial

METABOLIC—thyroid storm

STRUCTURAL

- **HEMORRHAGE**—subarachnoid, epidural, subdural, intracerebral
- **CEREBRAL INFARCT**
- **TUMOR**
- **PITUITARY APOPLEXY**
- **VASCULAR**—TTP/HUS, lupus, vasculitis, granulomatous angiitis

PATHOPHYSIOLOGY

ASSOCIATIONS WITH SPECIFIC ORGANISMS

- **AGE 0–4 WEEKS**—*S. agalactiae*, *E. coli*, *Listeria monocytogenes*, *K. pneumoniae*
- **AGE 1–23 MONTHS**—*S. agalactiae*, *E. coli*, *S. pneumoniae*, *H. influenzae*, *N. meningitidis*

PATHOPHYSIOLOGY (CONT'D)

- **AGE 2–50 YEARS**—*S. pneumoniae*, *N. meningitidis*
- **AGE >50 YEARS**—*S. pneumoniae*, *N. meningitidis*, *L. monocytogenes*, aerobic Gram-negative bacilli*
- **IMMUNOCOMPROMISED**—*Listeria*, aerobic Gram negative bacilli*
- **NEUROSURGERY/HEAD TRAUMA**—*S. aureus*, *S. epidermidis*, aerobic Gram-negative bacilli*
- **CSF SHUNT**—*S. aureus*, *S. epidermidis*, aerobic Gram negative bacilli*, diphtheroids
- **BASILAR SKULL FRACTURE**—*S. pneumoniae*, *H. influenzae*, group A Streptococci

*aerobic Gram-negative bacilli include *Klebsiella*, *E. coli*, *Serratia*, *and Pseudomonas*

RISK FACTORS FOR *S. PNEUMONIAE*—pneumonia, otitis media, mastoiditis, sinusitis, endocarditis, head trauma with CSF leak, alcoholism, splenectomy

RISK FACTORS FOR *L. MONOCYTOGENES*—extremes of age, alcoholism, malignancy, immunosuppression, diabetes, hepatic failure, renal failure, iron overload, collagen vascular disease, HIV

COMPLICATIONS—neurologic complications include herniation, stroke, vasculitis, acute cerebral hemorrhage, and aneurysm formation of cerebral vessels, with symptoms such as seizures, hearing loss, and neuropsychological impairment. Systemic complications include septic shock, pneumonia, and ARDS

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS ADULT PATIENT HAVE ACUTE MENINGITIS?

	Sens (%)	Spc (%)
History		
Headache	68	
Nausea and vomiting	52	
Neck pain	28	
Physical		
Fever	87	
Neck stiffness	80	
Altered mental status	69	
Focal neurological findings	21	
Rash	13	
Kernig sign (patient lying supine with hip flexed >90°. Extension of knee from this position elicits resistance or pain in lower back or posterior thigh)	9	100

CLINICAL FEATURES (CONT'D)

	Sens (%)	Spc (%)
Brudzinski sign (passive neck flexion in supine patient results in flexion of knees and hips)	–	–
Jolt accentuation of headache (patient turns head horizontally at a frequency of 2–3 rotations per second. Worsening headache represents positive sign)	97	60
Combination of Findings		
Classic triad (fever, neck stiffness, headache)	46	

UPDATE—individual findings are not sufficiently accurate to diagnose meningitis. Absence of all 3 signs of the classic triad of fever, neck stiffness, and altered mental status is *not* sufficiently sensitive to rule out a diagnosis of meningitis. Fever and neck stiffness are the most sensitive findings of the triad. Kernig and Brudzinski signs have low sensitivity but high specificity. Jolt accentuation of headache may be a useful adjunctive maneuver for patients with fever and headache but requires further validation

JAMA 1999 282:2

The Rational Clinical Examination. McGraw-Hill, 2009

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, Cr/urea, INR, PTT, AST, ALT, ALP, bilirubin, fibrinogen, urinalysis
- **MICROBIOLOGY**—blood C&S, sputum Gram stain/AFB/C&S, urine C&S
- **IMAGING**—CXR, head CT (see below)
- **LUMBAR PUNCTURE**—(1) cell count and differential; (2) Gram stain, C&S and AFB; (3) cell count and differential; (4) protein, glucose, lactate; (5) PCR for HSV, VZV, enteroviruses; (6) cytology

DIAGNOSTIC AND PROGNOSTIC ISSUES

LUMBAR PUNCTURE—suspect bacterial infection if high neutrophils, low glucose, high protein, positive culture. Suspect viral infection if high lymphocytes, *normal* glucose, and normal/high protein (**NEJM 2006 355:e12**)

- **OPENING PRESSURE**—normal is 60–250 mmH_2O. Causes of elevated opening pressure include meningitis, pseudotumor cerebri, intracranial hemorrhage, tumors, and idiopathic
- **CELL COUNT AND DIFFERENTIAL**—normal WBC is <5/mm^3. This can increase to 1000–5000/mm^3 for bacterial meningitis (neutrophils mainly) and 50–1000/mm^3 for viral meningitis (lymphocyte predominant). Other causes include seizure, intracerebral hemorrhage, tumor, and "traumatic tap" (correct by +1 WBC for every 500–1000 RBCs)
- **XANTHOCHROMIA**—lysed RBCs. Present in >90% of patients within 12 h of subarachnoid hemorrhage onset
- **GRAM STAIN**—sensitivity is 60–80% in untreated bacterial meningitis and 40–60% in partially treated cases
- **CULTURE**—gold standard with sensitivity of 70–85% in untreated bacterial meningitis and 50% in partially treated cases. Viral, TB, and fungal cultures may be done as well
- **PROTEIN**—normal is 0.18–0.58 g/L. Significantly elevated in bacterial meningitis and obstruction, variably elevated in fungal and TB infections, and only sometimes elevated in viral infections. Other causes include tumors, intracranial hemorrhages, multiple sclerosis, and Guillain–Barre syndrome
- **GLUCOSE**—normal is 2/3 of serum level, up to 16.7 mM [300 mg/dL]. Significantly lower in bacterial meningitis, mildly lower in fungal and TB infections, and usually normal in viral infections

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES: HOW DO I PERFORM A LUMBAR PUNCTURE AND ANALYZE THE RESULTS TO DIAGNOSE BACTERIAL MENINGITIS?

TECHNIQUE—"use of an **atraumatic needle** compared with a standard needle and use of a **26-gauge** standard needle compared with a 22-gauge standard needle have been shown to be associated with reduced risk of headache after lumbar puncture. **Reinsertion of the stylet** before needle removal should occur (ARR 11%). **Patients do not require bed rest** after the procedure"

	LR+
CSF analysis	
CSF blood glucose ratio ≤ 0.4	18
CSF glucose >2.2 mmol/L [>40 mg/dL]	23
CSF WBC ≥ 500/μL	15
CSF lactate ≥ 3.5 mmol/L [≥32 mg/dL]	21

JAMA 2006 296:16

CT HEAD—indicated before lumbar puncture only if age >60, immunocompromised, history of CNS disease, seizures within 1 week, focal neurological abnormalities, papilloedema, obtunded or unconscious, inability to answer two questions correctly, or inability to follow two commands correctly

NEJM 2001 345:24

PROGNOSIS—mortality rate is 19–26% for *S. pneumoniae* meningitis and 3–13% for *N. meningitidis* meningitis. Factors conferring poor prognosis include systemic compromise, ↓ level of consciousness, and *S. pneumonia*

NEJM 2004 351:18

MANAGEMENT

ACUTE—ABC, O_2, IV, intubation. Droplet precautions for suspect *N. meningitidis* infection

EMPIRIC ANTIBIOTICS—**steroid** if acute bacterial meningitis and *15–20 min before* first dose of antibiotics (*dexamethasone* 0.15 mg/kg or 10 mg IV q6h × 4 days). ***Cefotaxime*** 2 g IV q6h or ***ceftriaxone*** 2 g IV q12h. Add ***vancomycin*** 500–750 mg IV q6h if concerned about penicillin-resistant Pneumococci. Add ***ampicillin*** 2 g IV q4h if age >50 for *Listeria* coverage. If neurosurgery/trauma, CSF shunt, or basilar skull fracture, give ***ceftazidime*** 2 g IV q8h plus **vancomycin**. If HSV encephalitis, give ***acyclovir*** 10 mg/kg IV q8h

SPECIFIC ANTIBIOTICS—***S. pneumoniae*** (penicillin G or ampicillin if MIC <0.1 μg/mL, ceftriaxone or cefotaxime ± vancomycin × 10–14 days if MIC >1.0 μg/mL), ***N. meningitidis*** (ceftriaxone, penicillin G or ampicillin × 7 days), ***L. monocytogenes*** (ampicillin or penicillin G, plus gentamicin × 21 days), ***H. influenzae*** (ampicillin, ceftriaxone, or cefotaxime × 7 days), **Enterobacteriaceae** (ceftriaxone or cefotaxime × 7 days)

SPECIFIC ENTITIES

CHRONIC MENINGITIS (>4 weeks symptoms and persistent CSF abnormalities)—consider TB, fungal infections, neurosarcoidosis, lymphoma, and leptomeningeal carcinomatosis

RECURRENT MENINGITIS—**congenital predisposition** (myelomeningocele, dermal sinus), **acquired** (trauma, tumor, shunt), **immunologic defects** (complement defects, antibody defects, splenectomy)

HSV ENCEPHALITIS

- **PATHOPHYSIOLOGY**—usually infects the temporal lobe → subacute illness with fever, focal neurologic abnormalities, aphasia, mental status changes, and seizures. May have long-term sequelae
- **DIAGNOSIS**—lumbar puncture (mild lymphocytic pleocytosis <500 cells/μL, erythrocytes, xanthochromia, ↑ protein, normal glucose, PCR for HSV1 and HSV2), MRI (hyperintense lesion in the inferior medial temporal lobe, often extending into the insula)
- **TREATMENTS**—*acyclovir* 10 mg/kg/dose q8h × 14–21 days

WEST NILE VIRUS ENCEPHALITIS

- **PATHOPHYSIOLOGY**—flavivirus West Nile virus transmitted by mosquitoes between late spring and early autumn
- **CLINICAL FEATURES**—wide spectrum from asymptomatic (30%) to severe neurologic disorder (0.5%). Fever, erythematous rash, meningitis, encephalitis, and flaccid paralysis.

SPECIFIC ENTITIES (CONT'D)

Risk of progression to severe neurological disease about 1/150, highest in the elderly

- **DIAGNOSIS**—lumbar puncture (viral picture, PCR for West Nile virus), IgM antibody to West Nile virus in serum or cerebrospinal fluid (samples from the acute and convalescent phases, submitted at least 2 weeks apart)

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—supportive. Prevention is key (insect repellent, proper clothing)

Related Topics
Delirium (p. 432)
Infection Control (p. 304)

Urinary Tract Infections and Sexually Transmitted Infections

Urol Clin N Am 2008;35:1;
www.phac-aspc.gc.ca/std-mts/sti-its/guide-lignesdir-eng.php
CID 2011:52(5)

DIFFERENTIAL DIAGNOSIS OF DYSURIA

★SUV★

SEXUALLY TRANSMITTED DISEASES—*Chlamydia trachomatis*, *Neisseria gonorrhoeae*, HSV

URINARY TRACT INFECTIONS (urethritis, cystitis, pyelonephritis, perinephric abscess)—**bacterial** (**★KEEPS★** ***K****lebsiella*, ***E****. coli*, ***E****nterococci*, ***P****roteus*, ***S****taphylococcus saprophyticus*)

VAGINAL INFECTIONS—*Candida albicans*, Trichomonas, bacterial vaginosis

PATHOPHYSIOLOGY OF URINARY TRACT INFECTIONS

COMPLICATED UTI—presence of functional or anatomic abnormality of the urinary tract (polycystic kidney disease, nephrolithiasis, neurogenic bladder, diabetes, immunosuppression, pregnancy, indwelling urinary catheter, recent urinary tract instrumentation)

UNCOMPLICATED UTI—absence of risk factors above. In women, uncomplicated UTIs are usually treated for 3 days (or 5–7 days with nitrofurantoin)

PYELONEPHRITIS—usually 18–40-year-old women, fever, costovertebral angle tenderness, blood and urine cultures indicated. Challenges differentiating between cystitis and pyelonephritis

RISK FACTORS FOR UTI

- **YOUNG WOMEN**—frequent or recent sexual activity
- **ELDERLY WOMEN**—age, estrogen deficiency, incontinence, diabetes, cystoceles, previous GU surgery

PATHOPHYSIOLOGY OF CATHETER-ASSOCIATED BACTERIURIA—bacteria establish biofilm in or on catheter and enter bladder

PATHOPHYSIOLOGY OF URINARY TRACT INFECTIONS (CONT'D)

intra- or extraluminally. Common organisms include *E. coli* and enterococci. Responsible for 80% of urosepsis. Risk factors include duration of catheterization, errors in catheter care, diabetes mellitus, and female sex

CLINICAL FEATURES OF URINARY TRACT INFECTIONS

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS WOMAN HAVE ACUTE UTI?

	LR+	LR–
History		
Dysuria	1.5	0.5
Frequency	1.8	0.6
Hematuria	2.0	0.9
Fever	1.6	0.9
Flank pain	1.1	0.8
Lower abdominal pain	1.1	0.9
Vaginal discharge	0.3	3.1
Vaginal irritation	0.2	2.7
Back pain	1.6	0.8
Physical		
Vaginal discharge	0.7	1.1
CVA tenderness	1.7	0.9
Urine dipstick		
Leukocyte esterase or nitrite positive	4.2	0.3

APPROACH—"four symptoms (dysuria, frequency, hematuria, back pain) and one sign (CVA tenderness) increased the probability of UTI and may effectively rule in if all present. However, no combinations reliably rule out UTI. Urinalysis is moderately powerful and should be considered in women with appropriate urinary tract

CLINICAL FEATURES OF URINARY TRACT INFECTIONS (CONT'D)

symptoms. If the dipstick leukocyte esterase or nitrite is positive, the probability of UTI is high, especially when combined with other positive findings from the history and physical. If dipstick is negative but probability of disease is still relatively high, a urine culture should be considered to rule out infection"

JAMA 2002 287:20
The Rational Clinical Examination. McGraw-Hill, 2009

INVESTIGATIONS FOR URINARY TRACT INFECTIONS

BASIC

- **LABS**—CBCD, lytes, Cr/urea, urinalysis
- **MICROBIOLOGY**—urine C&S

DIAGNOSTIC ISSUES FOR URINARY TRACT INFECTIONS

NUMBER OF BACTERIA—significant bacteria ($>10^5$/mL) in clean catch suggests UTI (sens 50%). If using lower threshold to $>10^3$/mL for women with symptoms, sensitivity increases and specificity only decreases slightly

URINALYSIS—nitrite or leukocyte esterase (sens 75%, spc 82%), pyuria (sens 95%, spc 71%), bacteria (sens 40–70%, spc 85–95%). Not necessary if symptomatic uncomplicated UTI

URINE CULTURE—not always needed if symptomatic and biochemical evidence (i.e. leukocyte esterase) of uncomplicated UTI (see Clinical Features). However, antimicrobial resistance is increasing, so culture and sensitivity may become more important

MANAGEMENT OF URINARY TRACT INFECTIONS

UNCOMPLICATED UTI IN WOMEN—*trimethoprim–sulfamethoxazole* (DS-160/800 mg) 1 tab PO BID × 3 days, *ciprofloxacin* 250–500 mg PO BID × 3 days, *levofloxacin* 250–500 mg PO daily × 3 days, *nitrofurantoin macrocrystals* 50 mg PO QID × 5–7 days, *nitrofurantoin monohydrate macrocrystals* 100 mg PO BID × 5–7 days, *amoxicillin–clavulanate* 500 mg PO BID × 7 days, *fosfomycin trometamol* 3 g PO × 1 dose

COMPLICATED UTI—treatment duration 7–14 days

RECURRENT UTI (consider below measures if >3–4 episode of UTI/year)—**daily low-dose prophylaxis** (*trimethoprim–sulfamethoxazole DS* ½ tab PO qhs × 6 months, *nitrofurantoin* 50 mg or macrocrystals 100 mg PO qhs × 6 months), **post-coital prophylaxis** (*trimethoprim–sulfamethoxazole* DS ½-1 tab PO post-coital, *nitrofurantoin* 50 mg PO or *macrocrystals* 100 mg PO post-coital), **patient-initiated treatment** (start standard dose of antibiotics with onset of UTI symptoms)

SYMPTOM CONTROL—***phenazopyridine*** 100–200 mg PO TID × 2 days

ACUTE UNCOMPLICATED PYELONEPHRITIS—treat empircally with oral fluoroquinolones × 7 d (*ciprofloxacin* 500 mg PO BID or *levofloxacin* 750 mg PO daily). If isolate susceptible, may treat with trimethoprim–sulfamethoxazole, amoxicillin, or amoxicillin–clavulanate × 14 d. Most otherwise healthy, non-pregnant women with pyelonephritis can be treated on an outpatient basis. Otherwise, treat with IV antibiotics, at least initially (aminoglycoside ± ampicillin, third generation cephalosporin, or carbapenem)

CATHETER-ASSOCIATED BACTERIURIA—remove or replace catheter and initiate antibiotics for symptomatic infection; switch to intermittent catheterization

PREGNANCY AND UTI—urinalysis for all pregnant women at 16 weeks. Treat all bacteriuria with amoxicillin or nitrofurantoin × 3–7 days even if asymptomatic as there is a 20–40% risk of pyelonephritis. Avoid fluoroquinolones

VAGINITIS

CANDIDA—vulvovaginitis with cheesy vaginal discharge, intense itch. Diagnosis by microscopy with 10% KOH showing hyphae and budding yeast, pH 4–4.5 (normal). Treat with vaginal antifungal cream (3–14 days) or *fluconazole* 150 mg PO × 1 dose

TRICHOMONIASIS—profuse purulent greenish vaginal discharge, strawberry cervix. Diagnosis by microscopy showing motile trichomonads, pH 5–6. Treat with oral *metronidazole* 2 g as a single dose (treatment of sexual partners indicated)

BACTERIAL VAGINOSIS—gray, fishy-smelling vaginal discharge. Diagnosis made by amine odor when KOH added to the discharge, pH >4.5 and clue cells (vaginal epithelial cells coated with bacteria) seen on microscopy. Treat if symptomatic or pregnant with metronidazole or clindamycin, orally or vaginally

SEXUALLY TRANSMITTED INFECTIONS (STI)

URETHRITIS IN MEN/CERVICITIS IN WOMEN

- **PATHOPHYSIOLOGY**—*N. gonorrhea*, *Chlamydia trachomatis*, and other non-gonococcal (*Ureaplasma urealyticum*, *Mycoplasma genitalium*, *Trichomonas vaginalis*, HSV)
- **DIAGNOSIS**—Gram stain of discharge, urine for chlamydia/gonorrhea (nucleic acid amplification test, NAAT) or urethral/cervical swab for gonorrhea culture; offer syphilis and HIV testing
- **TREATMENTS**—anti-gonococcal (*cefixime* 400 mg PO × 1 or *ceftriaxone* 125 mg IM × 1 plus azithromycin 1 g PO × 1), anti-chlamydial (*azithromycin* 1 g PO × 1, or *doxycycline* 100 mg PO BID × 7 days). If gonorrhea identified, empirically treat for both gonococcus and chlamydia since dual infection is common. Dual therapy is recommended for gonorrhea due to increasing incidence of resistance to third generation cephalosporins. Trace and treat all partners within the last 60 days

SYPHILIS

- **PATHOPHYSIOLOGY**—*Treponema pallidum* infection. Risk factors include men who have sex with men (MSM), sex trade, HIV infection

SEXUALLY TRANSMITTED INFECTIONS (STI) (CONT'D)

- **PRIMARY SYPHILIS**—presents as chancre (painless, indurated, non-purulent ulcer) within 3–90 days
- **SECONDARY SYPHILIS**—develops within 2 weeks to 6 months, with symptoms such as fever, maculopapular rash, mucocutaneous lesions, alopecia, lymphadenopathy, meningitis, uveitis, and cranial neuritis
- **TERTIARY SYPHILIS**—develops after year(s) and may involve the heart (aortitis), eyes (iritis, Argyll Robertson pupil), bones/soft tissues (gummas), and neurologic system (general paresis, a rapidly progressive dementia with psychotic features and tabes dorsalis which affects posterior columns of the spinal cord and the dorsal roots, leading to pain episodes, decreased vibration and proprioception, absent reflexes, and bowel/bladder dysfunction)
- **DIAGNOSIS**—first-line diagnostic test of choice for a primary syphilitic chancre should be either DFA or PCR, if available. Otherwise, treponemal serologies are more sensitive and become positive earlier than non-treponemal serologies and would be preferred if primary syphilis is a consideration

Diagnostic Method	Test(s)	Utility
Direct visualization	Dark field microscopy	Traditional but availability is limited
Visualization with fluorescent Ab	DFA	Diagnosis of 1 ° syphilis Sensitive/specific
Molecular testing	PCR	Diagnosis of 1 ° syphilis. Most sensitive/specific but not readily available
Treponemal serology (presence of Ab against TP)	FTA-ABS TPPA MHA-TP TP-EIA INNO-LIA	Diagnosis of syphilis Sensitive; however, does not differentiate venereal from non-venereal treponematosis
Non-treponemal serology (presence of Ab against cardiolipin/lecithin)	VDRL RPR	Screening RPR titer helpful in staging, check for reinfection, treatment monitoring

Abbreviations: *DFA* direct fluorescent antibody, *EIA* enzyme immunoassay, *FTA-ABS* fluorescent treponemal antibody-absorption, *MHA-TP* microhemagglutination assay for antibody to TP, *PCR* polymerase chain reaction, *RPR* rapid plasma reagin test, *TP* treponema pallidum, *TPPA* TP particle agglutination assay, *VDRL* Venereal Disease Research Laboratory, *INNO-LIA* line immunoassay

SEXUALLY TRANSMITTED INFECTIONS (STI) (CONT'D)

- **TREATMENTS**—for primary, secondary and early latent (<1 year) syphilis, *benzathine penicillin G* 2.4 M units IM × 1 (preferred) or *doxycycline* 100 mg PO BID × 2 weeks. For late latent (>1 year) syphilis, gummatous and cardiovascular syphilis, *benzathine penicillin G* 2.4 M units IM q7days × 3 weeks. For neurosyphilis or syphilitic eye disease, give *benzathine penicillin G* 3–4 M units q4h IV × 10–14 days. Follow-up is essential. Treatment failure is defined as persistent symptoms or failure of serologic test to decline by 4 fold within 6 months

PELVIC INFLAMMATORY DISEASE

- **PATHOPHYSIOLOGY**—includes endometritis, tuboovarian abscess, salpingitis, and pelvic peritonitis. Most commonly due to *N. gonorrhoeae*, *C. trachomatis*, *M. hominis*, *U. urealyticum*; may involve endogenous (gut) organisms including anaerobes. Complications include infertility, ectopic pregnancy, and chronic pelvic pain

SEXUALLY TRANSMITTED INFECTIONS (STI) (CONT'D)

- **CLINICAL FEATURES**—lower abdominal pain, abnormal vaginal bleeding/discharge, and dyspareunia may be mild and non-specific. Findings include lower abdominal tenderness, adnexal tenderness, and cervical motion tenderness
- **DIAGNOSIS**—high index of clinical suspicion. Cervical swab and urine NAAT for Chlamydia and gonorrhea. Ultrasound. Pregnancy test
- **TREATMENTS**—**outpatients** (*ceftriaxone* 250 mg IM × 1 and *doxycycline* 100 mg PO BID × 14 days, or *levofloxacin* 500 mg PO daily × 14 days); add *metronidazole* 500 mg PO BID × 14 days if there are risk factors for anaerobic pathogens. **Inpatients** (*doxycycline* 100 mg PO q12h and *cefoxitin* 2 g IV q6h × 14 days, or *clindamycin* 900 mg IV q8h and *gentamicin* 1.5 mg/kg IV q8h × 14 days)

http://www.phac-aspc.gc.ca/std-mts/sti-its/cgsti-ldcits/index-eng.php

Soft Tissue Infections — NEJM 2007 357:4; IDSA Guidelines 2014

DIFFERENTIAL DIAGNOSIS

DISCRETE LOCALIZED CUTANEOUS INFECTIONS—**superficial** (impetigo, folliculitis, furunculosis), **deep** (carbuncles, subcutaneous abscesses)

SPREADING DIFFUSE CUTANEOUS INFECTIONS (involves deeper dermis and subcutaneous tissues)—erysipelas, cellulitis

DEEP SOFT TISSUE INFECTIONS—necrotizing fasciitis (polymicrobial, *S. pyogenes*), gas gangrene (*C. perfringens*)

PATHOPHYSIOLOGY

RISK FACTORS FOR CELLULITIS

- **COMPROMISED SKIN**—trauma, IDU, psoriasis, eczema, fungal disease (especially tinea pedis)
- **COMPROMISED SENSORY/PROPRIOCEPTIVE NERVES**—diabetic neuropathy
- **COMPROMISED BLOOD/LYMPHATIC VESSELS**—diabetes, malignancy, lymphatic or venous insufficiency, venectomy, radiation, prior cellulitis

CELLULITIS—acute spreading infection involving the dermis and subcutaneous tissue, mostly

PATHOPHYSIOLOGY (CONT'D)

caused by Staphylococci and group A *Streptococcus*. It usually presents as a swollen, erythematous plaque with illdefined border

ERYSIPELAS—superficial cellulitis involving the upper dermis and lymphatics, mostly caused by group A *Streptococcus*. It usually presents as a raised, erythematous plaque with well-demarcated border. It occurs more commonly in infants and elderly

RISK FACTORS FOR SKIN AND SOFT TISSUE INFECTIONS DUE TO MRSA/CA-MRSA—previous MRSA infection, hospitalization, or household contacts of known MRSA; street involved/shelters/incarceration, injection drug use, athletes, children/day care

COMMON PATHOGENS CAUSING CELLULITIS

- **MOST COMMON**—*S. pyogenes* (β-hemolytic group A *Streptococcus*), *S. aureus*, other β-hemolytic streptococci (B, C, G, and F)
- **SURGICAL WOUND**—*S. aureus*, *S. pyogenes*
- **HUMAN BITE**—oral anaerobes, *Eikenella corrodens*
- **ANIMAL BITE**—*Pasteurella multocida*, *Capnocytophaga canimorsus*
- **TICK BITE**—*Borrelia burgdorferi*, Tularemia
- **FRESHWATER**—*Aeromonas hydrophila*
- **SEAWATER**—*Vibrio vulnificus*
- **FISH EXPOSURE**—*Erysipelothrix rhusiopathiae*, *Streptococcus iniae*
- **HOT TUB**—*Pseudomonas aeruginosa* folliculitis

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE AN INFECTION OF A CHRONIC WOUND?

	LR+	LR–
Increasing pain	11–20	0.64–0.88
Foul odour	1.5–3.1	0.73–0.92
Discoloured granulation tissue	1.4–1.9	0.64–0.85
Erythema	1.4–1.7	0.66–0.88
Edema	0.87–2.3	0.51–1.0
Heat	0.80–1.1	0.98–1.0
Serous exudate	1.1–1.9	0.57–0.62
Purulent exudate	0.50–0.74	1.1–1.3
Delayed healing	1.0–2.3	0.29–0.96
IDSA criteria (purulent exudate or ≥2 of pain, erythema, heat, or edema)	0.96	1.0

PATHOPHYSIOLOGY (CONT'D)

APPROACH—increasing pain is the most useful clinical feature that increases the likelihood of chronic wound infection. However, classic signs of wound infection (e.g. purulent exudate, erythema, heat, edema) used in isolation are not helpful in diagnosing chronic wound infection

JAMA 2012 307:6

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, lactate (if suspicion of necrotizing fasciitis)
- **MICROBIOLOGY**—swab of portal of entry or any open draining wound for Gram stain and C&S, blood C&S (indicated only if systemic symptoms)

MANAGEMENT

TREAT UNDERLYING CAUSE—**incision and drainage of abscesses. Elevation** of affected area if possible, compression and skin hydration. **Antibiotics for mild cellulitis** (*cephalexin* 500 mg PO QID, *dicloxacillin* 500 mg PO QID, or *clindamycin* 150–300 mg PO QID×5–14 days); for **systemic toxicity or severe cellulitis** (*cefazolin* 1–2 g IV q8h, *ceftriaxone* 1 g IV q24h, *nafcillin* 1–2 g IV q4–6 h×7–14 days). For MRSA associated skin infections, consider *vancomycin* 1–2 g IV q12h, *trimethoprim/sulfamethoxazole* 1 DS tab PO BID, *daptomycin* 4–6 mg/kg IV daily, *tigecycline* 100 mg loading dose, then 50 mg IV q12h, *doxycycline* 100 mg PO BID, *linezolid* 600 mg PO/IV q12h. **For mild erysipelas**, consider *penicillin* 500 mg PO QID or *amoxicillin* 500 mg PO TID. For **severe erysipelas** with fevers and **chills**, consider *ceftriaxone* 1 g IV q24h or *cefazolin* 1–2 g IV q8h×5–14 days

SPECIFIC ENTITIES

NECROTIZING FASCIITIS

- **TYPES**—**type 1** (polymicrobial infections including Enterococci, *E. coli*, non-group A *Streptococcus*, *Klebsiella*, anaerobes. Mixed infections occurring postoperatively or in those with diabetes or peripheral vascular disease, e.g. Fournier's gangrene of perineum in diabetics), **type 2** (monomicrobial *Streptococcus pyogenes* "Group A strep"; rarely, CA-MRSA. May occur at any age and in healthy hosts following minor trauma, penetrating injury, laceration, varicella, IDU, or childbirth)

SPECIFIC ENTITIES (CONT'D)

- **PATHOPHYSIOLOGY** (**type 1**)—inoculation of ischemic or devitalized tissue → host immune system and antibiotics relatively ineffective → rapid spreading of infection to surrounding tissue → late signs include fever, crepitus, shock → complications include compartment syndrome, acute renal failure, sepsis. May be limb or life-threatening. May develop over a few hours
- **ASSOCIATIONS**—host (age >50, cancer, alcoholism, immunocompromised, malnutrition, obesity), compromised skin (burns, trauma, postoperative infection), compromised blood vessels (peripheral vascular disease, diabetes)
- **CLINICAL FEATURES**—typically happens over body areas with limited fibrous tissue (trunk, extremities). Pain disproportionate to physical findings. Gangrenous skin changes, bullae, tense edema, and crepitus may be seen as late signs
- **DIAGNOSIS**—high index of suspicion (pain >> physical findings). Plain X-ray to check for gas with type 1 necrotizing fasciitis. CT or MRI maybe useful. Early deep incisional biopsy is gold standard
- **TREATMENTS**—urgent **surgical debridement** of all necrotic tissue. Consider **IVIG** if significant hypotension in Group A *Streptococcus* necrotizing fasciitis. **Polymicrobial** *piperacillin–tazobactam* 4.5 g IV q8h plus *vancomycin* 1 g IV q12h, **Streptococcus** (*penicillin G* 4 MU IV q4h plus *clindamycin* 600–900 mg IV q8h)

Osteomyelitis

CAUSES

HEMATOGENOUS (monomicrobial)—*S. aureus*, coagulase-negative staphylococci, Gram-negative bacilli (*P. aeruginosa*, *Serratia*, *E. coli*), TB, fungi

CONTIGUOUS SPREAD FROM SOFT TISSUE OR JOINTS (polymicrobial)—*S. aureus*, coagulase negative Staphylococci, *S. pyogenes*, *Enterococcus*, Gram-negative bacilli, anaerobes

CONTIGUOUS SPREAD WITH GENERALIZED VASCULAR INSUFFICIENCY (polymicrobial)—*S. aureus*, *Streptococcus*, *Enterococcus*, *Proteus mirabilis*, *P. aeruginosa*, anaerobes

DIRECT INOCULATION THROUGH TRAUMA OR SURGERY (monomicrobial or polymicrobial)—may involve skin or environmental commensal organisms

PATHOPHYSIOLOGY

ROUTE OF INFECTION

- **HEMATOGENOUS**—mainly central (vertebrae, sternoclavicular, sacroiliac) and sometimes long bones (femur, tibia, humerus)
- **CONTIGUOUS SPREAD FROM SOFT TISSUE INFECTIONS**—trauma, surgery, orthopedic prosthesis, decubitus ulcer
- **CONTIGUOUS SPREAD FROM SOFT TISSUE INFECTIONS WITH GENERALIZED VASCULAR INSUFFICIENCY**—ischemic ulcers, diabetic ulcers

RISK FACTORS FOR OSTEOMYELITIS

- **SYSTEMIC**—diabetes, sickle cell disease (Salmonella)

PATHOPHYSIOLOGY (CONT'D)

- **LOCAL**—vascular compromise (arterial insufficiency, neuropathy venous stasis), orthopedic surgery

CLINICAL FEATURES

DIABETIC FOOT ULCER—either probing of bone or ulcer area above 2 cm^2 is associated with ~90% chance of having underlying osteomyelitis (sens 66%, spc 85%, PPV 89%, NPV 56%). Further noninvasive testing is unlikely to improve accuracy of diagnosis

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT WITH DIABETES HAVE OSTEOMYELITIS OF THE LOWER EXTREMITY?

Wagner grading scale

0—no open lesions; may have evidence of healed lesions or deformities
1—superficial ulcer
2—deeper ulcer to tendon, bone, or joint capsule
3—deeper tissues involved, with abscess, osteomyelitis, or tendinitis
4—localized gangrene of toe or forefoot
5—gangrene of foot (partial or total)

	LR+	LR–
Clinical gestalt		
Clinical judgment	9.2	0.70
Wagner grade >2	5.5	0.54

CLINICAL FEATURES (CONT'D)

	LR+	LR–
Physical		
Bone exposure	9.2	0.70
Positive probe to bone finding	6.4	0.39
Ulcer area >2 cm^2	7.2	0.48
Ulcer inflammation	1.5	0.84
Laboratory		
ESR ≥ 70 mm/h	11	0.34
Swab culture	1	1
Abnormal plain radiograph	2.3	0.63
Abnormal MRI	3.8	0.14

APPROACH—"an ulcer area >2 cm^2, a positive probe-to-bone test result, an ESR ≥70 mm/h, and an abnormal plain radiograph are helpful in diagnosing the presence of lower extremity osteomyelitis in patients with diabetes. A negative MRI result makes the diagnosis much less likely when all of these findings are absent. No single historical feature or physical examination reliably excludes osteomyelitis. The diagnostic utility of a combination of findings is unknown. The gold standard for diagnosis is bone biopsy"
JAMA 2008 299:7

SYMPTOMS

- **ACUTE OSTEOMYELITIS** (<2 weeks)—typically associated with bone pain, tenderness, warmth, swelling, febrile, and chills. Hip, vertebrae, and pelvis tend to manifest few signs and symptoms
- **SUBACUTE OSTEOMYELITIS** (weeks to few months)—longer duration of above symptoms, but less severe. Over time, draining sinus tracts, deformity, instability, and vascular/neurologic changes may develop
- **CHRONIC OSTEOMYELITIS** (>few months)—similar to subacute osteomyelitis

INVESTIGATIONS

BASIC

- **LABS**—CBCD, ESR (monitor disease progress if elevated), urinalysis
- **MICROBIOLOGY**—blood C&S, urine C&S
- **IMAGING**—plain films (specific but insensitive), three-phase bone scan (sensitive), CT, MRI (most sensitive and specific, particularly spine and diabetic foot), indium-labeled WBC scan (specific), US, bone marrow scan, dual tracer scan

SPECIAL

- **ULCER PROBING**
- **BONE BIOPSY**—C&S, AFB, TB culture, fungal culture, histology; generally required for vertebral osteomyelitis (CT-guided biopsy can provide microbiological diagnosis to guide therapy)
- **ANKLE BRACHIAL INDEX**—ischemic ulcers suspected

DIAGNOSTIC ISSUES

PLAIN FILMS—soft tissue swelling and gas, cortical destruction, periosteal new bone formation, foreign bodies, deformities, fractures, and soft tissue gas. Usually the first imaging to investigate for osteomyelitis. However, may not detect changes until after 2–3 weeks of infection. May help make diagnosis of osteomyelitis but never excludes it (sens 61%, spc 72%, PPV 80% for diabetic foot osteomyelitis)

BONE SCAN—more sensitive but less specific than plain films (sens 70–100%, spc 36% for diabetic foot osteomyelitis). Useful for ruling out osteomyelitis, but cannot make the diagnosis

INDIUM-LABELED LEUKOCYTE SCAN—better sensitivity and specificity (but still poor) than bone scans in diabetic foot. Since WBC accumulates in the marrow, the scan is less sensitive in areas with red marrow (vertebrae, pelvis). Excellent for fracture nonunion osteomyelitis (sens 91%, spc 97%)

MRI—provides great anatomic details, more sensitive and specific than bone scan. Imaging of choice for specific body sites (vertebrae, diabetic foot)

ULTRASOUND—fluid collection adjacent to the bone without intervening soft tissue, elevation of the periosteum by >2 mm, and thickening of the periosteum. Sensitivity and specificity uncertain

BONE BIOPSY—gold standard for osteomyelitis and generally required in vertebral osteomyelitis. Positive blood cultures and corresponding radiologic findings may support diagnosis and sometimes replace bone biopsy. Consider holding off antibiotic therapy if not life-threatening infection to facilitate identification of organisms. Organisms from superficial skin swabs have little correlation with the actual organisms growing inside the bone, except for *S. aureus*

Related Topic
Diabetes Mellitus (p. 381)

MANAGEMENT

HEMATOGENOUS—for vertebral osteomyelitis, need blood and bone cultures, then start empiric antibiotics with *cloxacillin* 2 g IV q4–6 h or *cefazolin* 2 g IV q8h. Consider *vancomycin* 15 mg/kg IV q12h if high local MRSA rates. Once organism identified, treat with specific antibiotic (total 6–12 weeks of antibiotics guided by susceptibility from time of biopsy or definitive surgery, with at least 2 weeks of IV therapy). If failed therapy, consider bone/soft tissue debridement and another 4–6 weeks of antibiotics after definitive surgery

CONTIGUOUS SPREAD WITHOUT VASCULAR INSUFFICIENCY—after orthopedic surgery and specimen collection, start *vancomycin* 15 mg/kg IV q12h. For sternal osteomyelitis, give *vancomycin* 15 mg/kg IV q12h, then switch to specific antibiotics (total 6 weeks of antibiotics from time of definitive surgery, usually intravenous for the duration)

CONTIGUOUS SPREAD WITH VASCULAR INSUFFICIENCY—polymicrobial. Base therapy on bone culture, empirical coverage should include anaerobes (e.g. carbapenems, piperacillin–tazobactam)

SPECIFIC ENTITIES

VERTEBRAL OSTEOMYELITIS

- **PATHOPHYSIOLOGY**—usually results from disc-space seeding through hematogenous dissemination, seeding from urinary tract, trauma, extension of infection from adjacent structures, or as a complication of spine and disc surgery. Risk factors include extraspinal infection site, urinary tract instrumentation, vascular catheter, hemodialysis, intravenous drug abuse, cancer, and diabetes mellitus
- **CLINICAL FEATURES**—severe back pain, limited function, and fever (52%)
- **DIAGNOSIS**—MRI, blood cultures. Bone biopsy generally required for confirmation and microbiological diagnosis to guide therapy
- **TREATMENTS**—*cloxacillin* 2 g IV q4–6 h or *cefazolin* 2 g IV q8h. Consider *vancomycin* 15 mg/kg IV q12h if high local MRSA rates

PROSTHETIC JOINT INFECTIONS

- **PATHOPHYSIOLOGY**—most commonly due to coagulase-negative staphylococci
- **TREATMENTS**—debridement with retention of prosthesis may be possible with early-onset infection (within 3 months of surgery), short duration of symptoms (<3 weeks) with no sinus tract, a stable implant *and* a causative organism susceptible to quinolones (or trimethoprim–sulfamethoxazole) and rifampin, which are given for 3 months (hips) to 6 months (knees) after an initial course of appropriate IV antibiotic therapy for at least 2 weeks. If debridement and retention are not appropriate, removal of the infected prosthesis with one-stage or two-stage exchange; IV antibiotic therapy is also provided for 6 weeks following the initial surgery

NEJM 2009 361:8

Septic Arthritis

See SEPTIC ARTHRITIS (p. 309)

Tuberculosis: Pulmonary

www.respiratoryguidelines.ca/tb-standards-2013; NEJM 2004 350:20

PATHOPHYSIOLOGY

ORGANISMS—genus *Mycobacterium* consists of >50 species. TB is caused by *M. tuberculosis* complex including *M. tuberculosis*, *M. bovis*, and others. The cell envelope contains mycolic acid → resists destaining by acid alcohol, thus termed acid fast bacilli

TRANSMISSION—TB transmission is almost exclusively airborne through inhalation of minute droplet nuclei. Therefore, lungs are the primary focus. However, any organs can become infected during the bacteremia that follows initial lung infection

LATENT TB INFECTION (LTBI)—follows initial infection; asymptomatic; detected by tuberculin skin test (TST) or interferon-gamma release assay (IGRA). Risk of active infection generally is 5% in the first 2 years with 5% risk of reactivation thereafter

PATHOPHYSIOLOGY (CONT'D)

FACTORS THAT INCREASE THE RISK OF INFECTION—1/3 of the world's population is infected with TB. Birth in endemic area (less commonly travel) is the major risk factor; other risk factors include aboriginal populations and racial/ethnic minorities, household/institutional contacts and crowding (healthcare workers, long-term care, correctional facilities, substance abuse, and shelters)

FACTORS INCREASING THE RISK OF REACTIVATION OF LTBI—HIV infection (most important risk factor, always test those with active TB for HIV), fibronodular disease on CXR, chronic renal failure, increasing age, malignancy, transplant/immunosuppression, silicosis, chronic steroid use, TNF-α inhibitors, alcohol abuse, malnutrition, liver or kidney disease, poorly controlled diabetes, smoking, gastrectomy, jejunoileal bypass

CLINICAL FEATURES

PRIMARY TB

- **SYMPTOMS**—fever, night sweats, pleuritic chest pain, chronic cough, anorexia, weight loss, fatigue, erythema nodosum
- **SIGNS**—often none. Primary TB usually involves the mediastinal lymph nodes (Ghon complex); hilar lymphadenopathy in the presence of *RML collapse* is the most common radiologic finding (2/3) with pleural effusion in 1/3. Lung infiltrates may be seen and involve lower lungs or middle lung fields most commonly with possible cavitation in areas of consolidation

REACTIVATION TB (active pulmonary)

- **SYMPTOMS**—subacute progressive cough, yellow-green sputum (increases over time), hemoptysis (25%), chest pain/dyspnea (33%), fever/night sweats (50%), fatigue (50–66%), weight loss
- **SIGNS**—reactivation TB usually involves the apical-posterior segments of upper lobes (80–90%), cavitation (19–40%), hilar lymphadenopathy (more likely than cavitation in AIDS patients)
- **ELDERLY WITH REACTIVATION TB**—presents with fever, night sweats, or hemoptysis less often. Lesions less often cavitary and less often TST positive

COMPLICATIONS OF PULMONARY TB—hemoptysis (rarely massive), pneumothorax (more common in endemic countries), bronchiectasis, and pulmonary destruction (rare)

Related Topic
Tuberculosis in Pregnancy (p. 473)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, albumin, urinalysis
- **MICROBIOLOGY**—blood C&S with mycobacterial culture, sputum Gram stain/AFB/C&S, urine AFB/C&S, HIV serology
- **IMAGING**—CXR, CT chest

SPECIAL

- **SKIN TEST**—see Diagnostic Issues for details
- **INTERFERON GAMMA RELEASE ASSAYS**—QuantiFERON-TB Gold In-Tube (QFT-GIT) assay and T-SPOT TB assay
- **PCR**
- **MOLECULAR FINGERPRINTING**—tracing outbreaks
- **SUSCEPTIBILITY TESTING**—1 extra week
- **THORACENTESIS**—if effusion. Send for fluid AFB and TB culture
- **PLEURAL BIOPSY**
- **CSF**—AFB, TB culture

DIAGNOSTIC ISSUES

TUBERCULIN SKIN TEST (TST)—gold standard for diagnosing latent tuberculosis (epidemiologic tool), but not sensitive or specific to include or exclude active pulmonary TB. Given as 5 units TST-S (purified protein derivative) intradermally, measure extent of induration after 48–72 h. Skin test reaction cutoffs and corresponding population groups when test considered positive (in North America) are as follows:

- **0–4 MM**—in general, considered negative; no treatment indicated unless child <5 years of age and high risk of TB infection
- **≥5 MM**—HIV positive, recent infectious TB contact within 2 years, CXR signs (fibronodular disease), immunosuppression (TNFα inhibitors, organ transplantation, glucocorticoid treatment equivalent of ≥15 mg/day prednisone × ≥1 month), end stage renal disease
- **≥10 MM**—all others, including TST conversion within 2 years, diabetes, malnutrition (<90% ideal body weight), cigarette smoking, daily alcohol consumption >3 drinks/day, silicosis, hematologic malignancies (leukemia/lymphoma) and certain carcinomas (e.g. head and neck, lung)

Canadian Tuberculosis Standards, 7th Edition 2013

INTERFERON GAMMA RELEASE ASSAYS—sens >95%; not affected by prior BCG vaccination. Most useful for evaluation of latent TB in those with positive TST and previously vaccinated with BCG

DIAGNOSTIC ISSUES (CONT'D)

SPUTUM SMEAR

- **UTILITY**—morning sputum × 3 days (AFB, TB culture), induced sputum if necessary, bronchoscopic lavage if cannot obtain sputum. Three consecutive AFB-negative sputum samples support that patient is non-infectious and can come off isolation
- **LIMITATIONS**—smear only detects 50% of culture positive TB, and in non-endemic areas positive smear may represent non-TB mycobacterium
- **STAINING AGENTS**—standard is Ziehl–Neelsen (acid fast stain); Auramine–Rhodamine or Auramine O fluorescence staining improves sensitivity but must be confirmed with acid fast

SPUTUM CULTURE—2–8 weeks in egg media, 4–14 days if radiometric (sens 80–85%, spc 98–99%)

POLYMERASE CHAIN REACTION (PCR)—more useful in non-endemic countries to rule out other common mycobacteria. High specificity but variable sensitivity (if AFB positive, sens 94–96%, spc 99.7–100%. If AFB positive, sens 9–100%, spc 25–100%)

MANAGEMENT

LATENT TB INFECTION—***isoniazid*** 300 mg PO daily × 6–12 months or ***rifampin*** 600 mg PO daily × 4 months. A "decision to tuberculin test is a decision to treat" with no age cutoff for treatment and regardless of BCG vaccination status. Exclude active TB with sputum culture and CXR before treatment. HIV, immunosuppressed, and newly infected patients should be priority for treatment of latent TB

PRIMARY OR REACTIVATION TB—patients should be isolated in single rooms with negative air pressure. TB therapy should be undertaken in consultation with an expert. Susceptibility testing is necessary to guide treatment. Directly observed treatment (DOT) is the standard of care for all patients. TB therapy consists of an intensive phase of daily therapy followed by a continuation phase of twice- or thrice-weekly therapy. ★**RIPE**★ ***Rifampin*** 10 mg/kg or 600 mg PO daily, ***isoniazid*** 5 mg/kg or 300 mg PO daily, ***pyrazinamide*** 20–25 mg/kg PO daily × 8 weeks. ***Ethambutol*** 15–20 mg/kg PO daily is added until drug susceptibility results are available. This is followed by isoniazid and rifampin daily, twice weekly, or three times weekly for 16 more weeks. Alternatives include isoniazid, rifampin, pyrazinamide, plus ethambutol or streptomycin

MANAGEMENT (CONT'D)

three times weekly for 24 weeks, or isoniazid, rifampin, pyrazinamide, plus ethambutol for 2 weeks, then twice weekly for 6 weeks, followed by isoniazid and rifampin twice weekly for 16 weeks (see guidelines for exceptions and alternate regimens when faced with resistance or drug intolerance)

TREATMENT ISSUES

VACCINATION WITH BCG (Bacillus Calmette-Guerin)—decreases miliary and meningeal TB by 75–86% and pulmonary TB by 50% in children. However, BCG leads to false-positive skin test, which may compromise contact tracing and decision to treat latent TB infection. Not routinely performed in areas with low endemic TB risk

DIRECTLY OBSERVED TREATMENT—most effective method to prevent multi-drug-resistant tuberculosis according to the WHO

MEDICATION DETAILS

- **RIFAMPIN** (RIF)—bactericidal. Side effects include hepatic toxicity (less than INH, but induces hepatic microsomal enzymes → ↑ clearance and ↓ effects of many drugs), flu-like symptoms, red-orange urine, sweat, tears
- **ISONIAZID** (INH)—bactericidal and inexpensive. Side effects include hepatitis (↑ with increased age and alcohol use), peripheral neuropathy (↓ with *pyridoxine* 10 mg PO daily or 25 mg PO daily if HIV, diabetes, malnourished, renal failure, pregnancy, or breast feeding)
- **PYRAZINAMIDE** (PZA)—bactericidal at acidic pH in cells. Side effects include GI intolerance, hepatic injury, hyperuricemia due to ↓ renal excretion, arthralgias
- **ETHAMBUTOL**—mostly bacteriostatic. Main side effect is optic neuritis

DRUG MONITORING

- **BASELINE**—platelet, Cr, AST, ALP, bilirubin, uric acid (pyrazinamide), visual acuity, and red-green color discrimination (ethambutol)
- **FOLLOW-UP**—symptoms of hepatotoxicity and visual disturbance

TREATMENT OF CO-INFECTION WITH TB AND HIV—similar treatment outcome with or without HIV, but treatment of active TB infection in HIV patients should be extended beyond 6 months if bacteriologic or clinical response is slow or suboptimal. Also beware of TB and HIV drug interactions (protease inhibitors and non-nucleoside reverse transcriptase inhibitors may cause toxic levels of rifampin, which should be replaced by rifabutin)

Approach to Gram Stain, Culture, and Sensitivity

GRAM-POSITIVE COCCI

CLUSTERS (catalase positive) (Staphylococci)
- **COAGULASE POSITIVE**—*S. aureus*
- **COAGULASE NEGATIVE**—*S. epidermidis*, *S. saprophyticus*, *S. hominis*, *S. lugdunesis*, *S. schleiferi*

PAIRS/CHAINS (catalase negative)
- **α-HEMOLYTIC STREPTOCOCCI**—*S. pneumoniae*, viridians group streptococci
- **β-HEMOLYTIC STREPTOCOCCI**—*S. pyogenes* (Group A strep), *S. agalactiae* (Group B strep), group C, F, G strep
- **ENTEROCOCCUS**—*E. faecalis*, *E. faecium*
- **OTHERS**—*Abiotrophia*, *Granulicatella* ("nutrient variant Strep"), *Leuconostoc*, *Lactococcus*, *Aerococcus*

ANAEROBIC—*Peptostreptococcus*, *Streptococcus*, *Peptococcus*, *Anaerococcus*

GRAM-POSITIVE BACILLI

ACID FAST (mycobacterium)—*M. tuberculosis*, *M. leprae*, *M. avium-intracellulare* complex, or non-tuberculous Mycobacteria (NTM, also known as mycobacteria other than TB [MOTT]). These organisms have Gram-positive-type cell walls, but do not stain Gram positive due to the waxy mycolic acids in the cell envelope

SPORE FORMING
- **AEROBIC**—*Bacillus anthrax*, *Bacillus cereus*
- **ANAEROBIC**—*Clostridium perfringens*, *C. difficile*, *C. botulinum*

NON-SPORE FORMING
- **AEROBIC**, **FACULTATIVE**, **AEROTOLERANT**—*Corynebacterium*/diphtheroids, *Lactobacillus*, *Listeria*, *Gardenerella*, *Nocardia*
- **ANAEROBIC**—*Actinomyces*, *Propionibacterium*, *Eubacterium*

BRANCHING BACILLI—★**ABCD**-**LMN**★ ***A****ctinomyces* (acid fast negative), ***B****acillus*, ***C****lostridium*, **D**iphtheroids, ***L****isteria*, ***L****actobacillus*, ***M****ycobacterium* (modified and Ziehl–Neelsen acid fast), ***N****ocardia* (modified acid fast)

GRAM-NEGATIVE COCCI

NEISSERIA—*N. meningitidis* (diplococci), *N. gonorrhoeae* (diplococci), other Neisseria

MORAXELLA—*M. catarrhalis*

GRAM-NEGATIVE BACILLI

AEROBIC
- **GLUCOSE FERMENTING AND LACTOSE FERMENTING**—a number of Enterobacteriaceae including *E. coli*, *Citrobacter*, *Enterobacter*, *Klebsiella*, *Serratia*
- **GLUCOSE FERMENTING BUT NON-LACTOSE FERMENTING**—*Shigella*, *Salmonella*, *Hafnia*, *Morganella*, *Proteus*, *Yersinia*, *Edwardsiella*, *Vibrio* (oxidase positive), *Aeromonas* (oxidase positive), *Pleisiomonas* (oxidase positive)
- **NON-GLUCOSE AND NON-LACTOSE FERMENTING**
  - **OXIDASE POSITIVE**—*Pseudomonas*, *Ralstonia*, *Burkholderia*, *Roseomonas*, *Sphingomonas*
  - **OXIDASE NEGATIVE**—*Stenotrophomonas*, *Acinetobacter*, *Chryseomonas*

ANAEROBIC—*Bacteroides fragilis*, *Fusobacterium*, *Prevotella*, *Porphyromonas*

OTHERS—*Eikenella**, *Pasteurella* (cats), *Capnocytophaga* (dogs), *Kingella**, *Actinobacillus**, *Cardiobacterium**, *Haemophilus** (coccobacilli, pleomorphic), *Legionella* (BCYE agar), *Campylobacter* (boomerang)

*HACEK organisms in endocarditis

SPECIFIC ORGANISMS

NON-GRAM-STAINABLE—Chlamydia, Mycoplasma, Ureaplasma, Rickettsia, Treponema, Coxiella, Ehrlichia, Mycobacteria

ANTIBIOTIC SUSCEPTIBILITY AND RESISTANCE

GROUP A STREPTOCOCCAL INFECTIONS—resistant to clindamycin

STREPTOCOCCUS PNEUMONIAE—may develop resistance to penicillin by altered penicillin-binding protein

ANTIBIOTIC SUSCEPTIBILITY AND RESISTANCE (CONT'D)

S. AUREUS (MSSA)—may develop resistance to penicillin by β-lactamase

PSEUDOMONAS—various intrinsic mechanisms conferring resistance. Need to treat with dual antibiotic therapy for serious infections if therapy for >2 weeks or if susceptibility not yet available

VRE—vancomycin-resistant enterococci

MRSA—*S. aureus* that is resistant not only to penicillin, but also penicillinase-resistant penicillins (methicillin, nafcillin, oxacillin). In general, hospital MRSA strains have broader resistance (e.g. clindamycin, trimethoprim–sulfamethoxazole, tetracyclines) than community-associated MRSA strains (CA-MRSA). Risk factors for hospital MRSA infections include frequent hospital visits and contact with MRSA-infected individuals; CA-MRSA is associated with crowding, acute and chronic skin disease, poor hygiene, sharing of contaminated items, contact sports, and IDU

β-LACTAMASE-RESISTANT BACTERIA—**constitutive** (*E. coli**, *Klebsiella**, *Haemophilus*, *Neisseria*, *bacteroides*), **inducible** (*S. aureus*, ***S****erratia*†*, ***P****rovidencia*†, ***P****seudomonas*, **I**ndole-positive *Proteus*†*, ***C****itrobacter*†*, ***E****nterobacter*†*, ***H****afnia*†*, ***A****cinetobacter*†*, ***M****organella*†*)

†★**SPICE-HAM**★ organisms with inducible, chromosomally mediated cephalosporinases (AmpC type β-lactamases) resistant to penicillins, first and second generation cephalosporins, cephamycins, and β-lactamase inhibitors

*These organisms may have extended spectrum β-lactamase (ESBL) resistant to all β-lactams except carbapenems

GENTAMICIN AND TOBRAMYCIN DOSING

TOXICITY—nephrotoxicity, ototoxicity, neuromuscular blockade (rare). Serum aminoglycoside levels correlate with nephrotoxicity

LOADING DOSE (TRADITIONAL DOSING: Q8H)—dependent on indication. For mild infection, uncomplicated UTI, synergy with β-lactams for Gram positive infections, give 0.6–1.2 mg/kg IV q8h. For serious Gram-positive infection or sepsis, give 2.5 mg/kg IV. For life-threatening infections, give 3.0 mg/kg IV

MAINTENANCE DOSE (TRADITIONAL DOSING: Q8H)

- **START**—1.7 mg/kg IV q8h. Monitor serum levels after steady state reached; i.e. 3–5 half-lives (after third dose). Monitor renal function and ototoxicity every 3 days
- **PEAK LEVELS**—obtain 30–45 min after end of infusion. Should be 4.2–8.4 μmol/L [2–4 μg/mL] when drug is being given for synergy or uncomplicated infections, 12.6–16.8 μmol/L [6–8 μg/mL] for serious Gram-negative infection or sepsis, and 14.7–18.9 μmol/L [7–9 μg/mL] for life-threatening infections
- **TROUGH LEVELS**—obtain 0–30 min prior to scheduled dose. Should be <4.2 μmol/L [<2 μg/mL] to prevent toxicity
- **ADJUSTMENTS**—dosing interval is dependent on renal function (CrCl >60 mL/min, q8h; 40–60 mL/min, q12h; 20–40 mL/min, q24h; <20 mL/min single dose then measure serum concentration and give PRN). Changes in dose without changes in interval will result in proportional changes in both peak and trough serum drug concentrations. Prolongation of dosing interval will also reduce both, but particularly trough level

GENTAMICIN AND TOBRAMYCIN DOSING (CONT'D)

ANTIBIOTICS

Antibiotics	Mechanism	Gram positive	Gram negative	Anaerobes	Others	Renal adjustments
Penicillins						
Penicillin G 2–4 M units IV q4–6 h	Bactericidal, cell wall synthesis inhibition and lysis	++ Strep	Meningococcus	++	Syphilis	Yes (dose + interval)
Penicillin V 250–500 mg PO TID/QID		++ Strep		++		Yes (dose + interval)
Cloxacillin/nafcillin/oxacillin 1–2 g IV q4–6 h		++S. aureus				No
Amino-Penicillins						
Ampicillin 1–2 g IV q4–6 h	Bactericidal, cell wall synthesis inhibition and lysis	+++Strep/Entero	+/−H. flu, +/−*E coli*		*Listeria*	Yes (interval)
Amoxicillin 250–1,000 mg PO TID		+++Strep/Entero	+/−H. flu, +/−*E coli*			Yes (interval)
Amox/clavulanate 875/125 mg PO BID		+++Strep/Entero	++H. flu, *E coli*	+++		Yes (interval)
Anti-pseudomonal Penicillins						
Piperacillin 3–4 g IV q4–6 h	Bactericidal, cell wall synthesis inhibition and lysis	++	++Pseudo	++		Yes (dose + interval)
Pip/tazo 3.375 g q6h–4.5 g IV q8h		++Staph	++Pseudo/H. flu	+++		Yes (dose + interval)
Ticarcillin 3–4 g IV q4–6 h		++	++Pseudo	++		Yes (dose + interval)
Ticarcillin/clavulanate 3.1 g IV q4–6 h		++	++Pseudo	+++		Yes (dose + interval)
Monobactam and Carbapenems						
Aztreonam 1–2 g IV q6–8 h	Bactericidal, cell wall synthesis inhibition and lysis		+++Pseudo	+++		Yes (dose)
Imipenem 500 mg IV q6h		+++	++Pseudo	+++		Yes (dose + interval)
Meropenem 1 g IV q8h		++	+++Pseudo	+++		Yes (dose + interval)
Ertapenem 1 g IV q24h		++	++(no Pseudo)	+++		Yes (dose)
Doripenem 500 mg IV q8h		++	+++	+++		Yes (dose + interval)
First-Generation Cephalosporins						
Cefazolin 1–2 g IV q8h	Bactericidal, cell wall synthesis inhibition and lysis	+++	+			Yes (interval)

GENTAMICIN AND TOBRAMYCIN DOSING (CONT'D)

Antibiotics	Mechanism	Gram positive	Gram negative	Anaerobes	Others	Renal adjustments
Cephalexin 250–1000 mg PO QID		+++	+			Yes (interval)
Second-Generation Cephalosporins						
Cefuroxime 750–1500 mg IV q8h	Bactericidal, cell wall synthesis inhibition and lysis	++	++			Yes (interval)
Cefuroxime 125–500 mg PO BID		++	++			Yes (interval)
Cefprozil 250–500 mg PO q12h		++	++			Yes (interval)
Cefaclor 250–500 mg PO BID		++	++			Yes (interval)
Third/Fourth Generation Cephal.						
Cefoxitin 1–2 g IV q6–8 h	Bactericidal, cell wall synthesis inhibition and lysis	+++	+++	++		Yes (interval)
Cefotaxime 1–2 g IV q6–8 h		+++	+++			Yes (interval)
Ceftriaxone 1–2 g IV q24h		+++	+++			No
Ceftazidime 1 g IV q8–12 h		+++	+++Pseudo			Yes (interval)
Cefepime 1–2 g IV q12h		+	+++Pseudo			Yes (interval)
Cefixime 400 mg PO daily		+	++			Yes (interval)
Ceftaroline 600 mg IV q8–12 h		+++MRSA	+++			Yes (interval)
Aminoglycosides						
Gentamicin 5–7 mg/kg IV q24h	Bactericidal, binds to 30S and 50S ribosomes	Entero (syn)	+Pseudo			Yes (dose + interval)
Tobramycin 5–7 mg/kg IV q24h		+/–Entero (syn)	++Pseudo			Yes (dose + interval)
Amikacin 7.5 mg/kg q12h		+/–Entero (syn)	++Pseudo			Yes (dose + interval)
Streptomycin 15 mg/kg IM or IV q24h		Entero (syn)	++Pseudo	AFB, Plague		Yes (dose + interval)
Fluoroquinolones						
Ciprofloxacin 500 mg PO/400 mg IV BID	Bactericidal, inhibit DNA synthesis through inhibition of DNA gyrase and topoisomerase		+++Pseudo		AFB	Yes (interval)
Norfloxacin 400 mg PO BID			+++			Yes (dose ± interval)

GENTAMICIN AND TOBRAMYCIN DOSING (CONT'D)

Antibiotics	Mechanism	Gram positive	Gram negative	Anaerobes	Others	Renal adjustments
Ofloxacin 200–400 mg PO BID			++		AFB	Yes (dose ± interval)
Levofloxacin 500–750 mg PO/IV daily		++	+++		AFB	Yes (dose ± interval)
Moxifloxacin 400 mg PO/IV daily		++	+++	++	AFB	Yes (dose ± interval)
Gemifloxacin 320 mg PO daily		++	+++		AFB	Yes (dose ± interval)
Macrolides						
Azithromycin 250 mg PO daily	Bacteriostatic, binds to 50S ribosomes	+	+H. flu/legion		++Mycoplasma and *Chlamydia* for all macrolid es	No
Clarithromycin 250–500 mg PO BID		+	+H. flu/legion			Yes (dose)
Erythromycin 250–500 mg PO q6–12 h		+	+Legion			No
Tetracyclines						
Doxycycline 100 mg PO/IV q12h	Bacteriostatic, binds to 30S ribosomes		+		+*Chlamydia*	No
Minocycline 50–100 mg PO daily-BID		+	+		+*Chlamydia*	No
Tetracycline 500 mg PO QID			+		+*Chlamydia*	Avoid
Tigecycline 100 mg IV, then 50 mg q12h		+++MRSA, VRE	++Acinetobacter		+*Chlamydia*	No
Sulfa						
Sulfamethoxazole/Trimethoprim 1–2 SS/DS tab PO BID (also available IV)	Bactericidal, blocks DNA synthesis	+	++Steno, +PJP			Yes (interval)
Clindamycin						
Clindamycin 150–450 mg PO QID or 300–600 mg IV q6–12 h	Bacteriostatic, binds to tRNA complex	++		+++		No
Metronidazole						
Metronidazole 500 mg PO/IV q12h	Bactericidal, DNA breakage		*H. pylori*, *G. vaginalis*	+++C. diff	++protozoa	No

GENTAMICIN AND TOBRAMYCIN DOSING (CONT'D)

Antibiotics	Mechanism	Gram positive	Gram negative	Anaerobes	Others	Renal adjustments
Glycopeptides						
Vancomycin 15 mg/kg IV q12h	Bactericidal, interferes with peptidoglycan and RNA synthesis	+++				
		S. epidermidis, MRSA, Entero		++C. diff		Yes (interval)
Oxazolidinones						
Linezolid 600 mg PO/IV q12h	Bactericidal (Strep) and bacteriostatic (Staph, entero), binds to 50S ribosomes	++MRSA, VRE		+	++AFB	No
Streptogramins						
Quinupristin/dalfopristin 7.5 mg/kg IV q8h via central line	Inhibits late + early protein synthesis	++MRSA, VRE (not *E. faecalis*)		+		No
Lipopeptides						
Daptomycin 4–6 mg/kg q24h	Bactericidal, disrupts cell membrane	++MRSA, VRE		+		Yes (interval)

ONCE-DAILY GENTAMICIN AND TOBRAMYCIN DOSING

RATIONALE—optimize treatment of Gram-negative infections with less nephrotoxicity than q8h dosing. Similar ototoxicity and neuromuscular toxicity

NOT RECOMMENDED—monotherapy for infections outside urinary tract, pregnant patients, dialysis patients, endocarditis, CNS infections, osteomyelitis, ophthalmologic infections, surgical prophylaxis, patients with rapid drug clearance (e.g. burns >20% BSA), Gram-positive infections, patients receiving concurrent ototoxins (e.g. furosemide) neonates, pediatric patients with significant renal dysfunction, duration of therapy >14 days

LOADING DOSE—5–7 mg/kg IV

MAINTENANCE DOSE (5–7 mg/kg IV q24–48 h)

- **START**—monitor serum level 6–14 h after first dose. Monitor renal function and ototoxicity q3d
- **ADJUSTMENTS**—dosing interval (q24–48 h) is based on 6–14 h serum level (Hartford nomogram, **Antimicrob Agents Chemother 1995 39:3**). Pharmacy consult to assist with dosing (once daily dosing provides peak levels of 15–31–46 μmol/L [22 μg/mL] and trough levels <2.1 μmol/L [<1 μg/mL] to prevent toxicity. Peak and trough levels do not need to be monitored)

DOSING WEIGHT FOR AMINOGLYCOSIDES—for obese patient (i.e. actual body weight (BW) >125% of ideal body weight (IBW)), use adjusted body weight (ABW) for dose determination:

- **ABW** (kg) = IBW +0.4(BW-IBW)

Note: 1 kg = 2.2 lbs. See p. 460 for IBW calculation

Related Topic
Drug Eruptions (p. 422)

VANCOMYCIN TOXICITY AND DOSING

TOXICITY—rash, infusion-related red man syndrome, rarely nephrotoxicity (especially combined with aminoglycoside), and ototoxicity. However, serum vancomycin levels do not predict toxicity

LOADING DOSE—15–20 mg/kg (usually 1–1.5 g) IV

VANCOMYCIN TOXICITY AND DOSING (CONT'D)

MAINTENANCE DOSE—30 mg/kg (actual body weight) per day divided into 2–4 doses (maximum usually 1.5 g/dose)

- **START**—monitoring after steady state, i.e. after third dose normally, or after second dose if dosing interval >48 h. Monitor only if treatment duration >14 days in patients with stable renal function and mild/moderate infection, or treatment duration >4 days in patients with unstable renal function or severe infection
- **TROUGH LEVELS**—obtained 30–60 min before next scheduled dose. Should be at least 6.9–10.4 μmol/L [10–15 μg/mL]; adjust to 10.4–13.8 μmol/L [15–20 μg/mL] for serious infections (endocarditis, osteomyelitis)
- **PEAK LEVELS**—there is no correlate for efficacy or toxicity and therefore should not be monitored
- **ADJUSTMENTS**—dosing interval is dependent on renal function (CrCl >100 mL/min, q12h; 80–100 mL/min, q18h; 60–80 mL/min, q24h; 40–60 mL/min, q36h; 25–40 mL/min q48h; <25 mL/min, single dose then measure serum concentration and give PRN). Changes in dose without changes in interval will result in proportional changes in both peak and trough serum drug concentrations. Prolongation of dosing interval will also reduce both, particularly trough level

PENICILLIN ALLERGY

HISTORY—characterize reaction (age when reaction occurred, timing of reaction after penicillin administration, type of reaction, route of administration, reason for penicillin, any other medications at the time, resolution), any similar antibiotics since

CROSS-REACTIVITY—incidence of cross-reactivity to cephalosporins when patient has penicillin allergy by history is <2%. Carbapenems and first/secondgeneration cephalosporins have higher cross-reactivity in the penicillin allergic than third-generation cephalosporins and aztreonam. It is often safe to use these medications, with the first dose monitored. If safety unclear, skin testing provides reassurance. For patients with a history of penicillin allergy, those with positive and negative skin test have 5.6% and 1.7% chance of developing cross-reactivity with cephalosporin, respectively

PENICILLIN ALLERGY (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES: IS THIS PATIENT ALLERGIC TO PENICILLIN?

HISTORY—history of penicillin allergy for predicting positive response to penicillin skin test result (LR+ 1.9, LR– 0.5), for predicting allergic response (anaphylaxis, positive skin test, or response to second course of penicillin [LR+ >11, LR– 0.98]).

TYPES OF ALLERGIC REACTIONS

★ACID★ ANTIBODY-MEDIATED (IgE), **C**ytotoxic (antibody-dependent), **Immune-complex-mediated**, **D**elayed hypersensitivity reaction

TYPE I—immediate <1 h, IgE antibodies mediated, anaphylaxis, hypotension, laryngeal edema, wheezing, angioedema, urticaria

TYPE II— > 72 h, IgG and complement mediated, increased clearance of RBC and platelets by lymphoreticular system

TYPE III— > 72 h, IgG and IgM immune complexes mediated, serum sickness, tissue injury

TYPE IV— > 72 h, contact dermatitis

PENICILLIN ALLERGY (CONT'D)

OTHERS— > 72 h, maculopapular or morbilliform rashes

APPROACH—"only 10–20% of patients reporting a history of penicillin allergy are truly allergic when assessed by skin testing. Taking a detailed history of a patient's reaction to penicillin may allow clinicians to exclude true penicillin allergy, allowing these patients to receive penicillin. Patients with a concerning history of type I penicillin allergy who have a compelling need for a drug containing penicillin should undergo skin testing. Virtually all patients with a negative skin test result can take penicillin without serious sequelae"

JAMA 2001 285:19

UPDATE—patients with a negative skin test result may still react to a repeat course of penicillin (~10%) but the likelihood of a life-threatening reaction is greatly reduced. Patients with a well-documented immediate reaction to penicillin are ~90% likely to react with subsequent courses

The Rational Clinical Examination. McGraw-Hill, 2009

Approach to Empiric Antibiotics

GENERAL APPROACH

CHOICE OF EMPIRIC ANTIBIOTIC—based on the most likely and deadly organisms for each type of infection. Thus, a good understanding of the pathophysiology of each infection and the local resistance pattern of various organisms is essential

CULTURE AND SUSCEPTIBILITY—should always be performed to facilitate targeted antibiotic treatment except for mild infections. However, the specific organism may not be identified even if multiple cultures are taken. In this case, the clinician must rely on clinical judgment and continue treatment with empiric antibiotic(s)

SPECIFIC INFECTIONS AND EMPIRIC ANTIBIOTIC CHOICES

SEPSIS—depending on the suspected source. For pulmonary source, respiratory fluoroquinolone plus ceftriaxone ± vancomycin if community setting, anti-pseudomonal plus ciprofloxacin if hospital setting. For urinary source, ceftriaxone or carbapenem or fluoroquinolone or aminoglycoside. For intra-abdominal source, piperacillin–tazobactam or a carbapenem. Duration of treatment is at least 10–14 days with rationalization of antibiotics when susceptibility results available. See p. 108 for details

SPECIFIC INFECTIONS AND EMPIRIC ANTIBIOTIC CHOICES (CONT'D)

MENINGITIS (*S. pneumoniae*, *N. meningitidis*, *Listeria*, HSV)—ceftriaxone/cefotaxime ± ampicillin ± vancomycin. Add acyclovir if CSF suggests viral picture. Duration of treatment is 7–21 days. See p. 269 for details

COMMUNITY–ACQUIRED PNEUMONIA (*S. pneumoniae*, *Klebsiella*, *Mycoplasma*)—macrolides ± cefotaxime or respiratory fluoroquinolones. Duration of treatment is usually 7 days. See p. 7 for details

ASPIRATION PNEUMONIA (anaerobes, Staph, GNB)—levofloxacin plus metronidazole. Duration of treatment is usually at least 7 days. See p. 7 for details

ICU/VENTILATOR-ASSOCIATED PNEUMONIA (GNB, *Pseudomonas*)—ciprofloxacin plus ceftazidime or piperacillin–tazobactam or carbapenem. Duration of treatment is usually 8 days (p. 105)

SPECIFIC INFECTIONS AND EMPIRIC ANTIBIOTIC CHOICES (CONT'D)

ENDOCARDITIS (*S. aureus*, *S. viridans*, *Enterococcus*)Duration of treatment is highly variable. See AHA guidelines and p. 60 for details

- **NATIVE VALVE DISEASE**—ampicillin + cloxacillin/nafcillin or vancomycin plus gentamicin
- **INJECTION DRUG USE**—cloxacillin or vancomycin plus gentamicin
- **PROSTHETIC VALVE DISEASE**—vancomycin plus gentamicin

ACUTE BLOODY DIARRHEA (*Salmonella*, *Shigella*, *Campylobacter*)—ciprofloxacin. Duration of treatment is 3 days. See p. 137 for details

ANTIBIOTIC-ASSOCIATED DIARRHEA (*C. difficile*)—oral metronidazole. Duration of treatment is 10 days. See p. 138 for details

PERITONITIS/INTRA-ABDOMINAL SEPSIS (coliforms, anaerobes)—pipericillin–tazobactam, imipenem, or ampicillin plus ciprofloxacin plus metronidazole. Treat until WBC/peritonitis resolved

FEVER IN SPLENECTOMIZED PATIENT (*H. influenza*, *N. meningitidis*, *S. pneumoniae*, *Capnocytophaga canimorsus*)—cefotaxime/ceftriaxone. Duration of treatment is usually 10–14 days. See p. 164 for further information

URINARY TRACT INFECTION (*E. coli*, *Klebsiella*, *Enterococcus*, *Proteus*, *S. saprophyticus*)—nitrofurantoin, trimethoprim–sulfamethoxazole, ciprofloxacin, fosfomycin. Duration of treatment is 3 days if uncomplicated UTI, otherwise 14–21 days. See p. 272 for details

CELLULITIS (*Staphylococcus*, *Streptococcus*)—cefazolin, cloxacillin, or cephalexin. Vancomycin if MRSA suspected. Duration of treatment is usually 7–10 days. See p. 275 for details

HUMAN BITE (Gram positive, *Eikenella*, anaerobes)—amoxicillin–clavulanate, or clindamycin plus ciprofloxacin

DIABETIC FOOT (polymicrobial)—amoxicillin–clavulanate or ciprofloxacin plus clindamycin, or trimethoprim–sulfamethoxazole plus metronidazole. Treat until resolution. May require IV antibiotics with *Pseudomonas* coverage (e.g. pipericillin–tazobactam; carbapenem). Osteomyelitis likely if ulcer >2 cm^2 or probe touches bone. See p. 277 for details

NECROTIZING FASCIITIS—surgical treatment is mandatory. For polymicrobial infection, cefotaxime plus clindamycin, pipericillin–tazobactam, or ampicillin/penicillin G plus ciprofloxacin/gentamicin plus metronidazole. For *Streptococcus*, penicillin G plus clindamycin. See p. 275 for details

OSTEOMYELITIS (Gram positive, Gram negative, anaerobes)—for Gram-positive coverage, cefazolin, or vancomycin. For Gram-negative coverage, ceftriaxone or ciprofloxacin. For *Pseudomonas*, piperacillin or carbapenem or ceftazidime, plus ciprofloxacin or aminoglycoside. Duration of therapy usually at least 6 weeks. See p. 277 for details

SEPTIC ARTHRITIS—vancomycin, cloxacillin, or cefazolin for Gram-positive coverage, ciprofloxacin or ceftriaxone for Gram-negative coverage. Usual duration 4 weeks. See p. 309 for details

Hepatitis B

See HEPATITIS B (p. 145)

Hepatitis C

See HEPATITIS C (p. 147)

Herpes Simplex Virus Infection

See HERPES SIMPLEX VIRUS (p. 416)

Human Immunodeficiency Virus http://aidsinfo.nih.gov/guidelines

RISK FACTORS FOR HIV

SEXUAL CONTACT
PARENTERAL—IDU, transfusion, or unsafe needle use in developing world, health workers
MATERNAL–FETAL—in-utero, delivery, breast feeding

ACUTE HIV INFECTION

STRAINS—HIV1 globally; HIV2 mainly in West Africa
SYMPTOMS—acute febrile "mononucleosis-like" illness, lymphadenopathy, pharyngitis, rash and headache within 1–6 weeks post-exposure. Hematologic (lymphopenia, thrombocytopenia) and liver enzyme abnormalities
DIAGNOSIS—ELISA assay (sens ~100%, spc <100%) → if positive, repeat ELISA → if positive, Western blot → if indeterminate, repeat Western blot 4 weeks, 3 months, and 6 months later. If during window period (2 weeks postexposure), may perform viral load testing
BASIC WORKUP FOR THE NEWLY DIAGNOSED

- **HIV STATUS**—viral load, CD4 count, genotypic antiretroviral drug resistance testing
- **BASELINE**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, TSH, glucose, fasting lipid profile, lipase, CK, HLA B*5701 (for abacavir hypersensitivity), βhCG, CXR, ECG, urinanalysis
- **CO-EXISTING/OPPORTUNISTIC INFECTIONS**—HAV serology, HBV testing (HBsAg, HBsAb, HBcAb. If HBsAg or HBcAb positive, check HBV DNA as well), HCV testing (HCV antibodies). If HCV positive, HCV RNA, assess genotype and order fibroscan. Pap smear, anal screening for HPV in men who have sex with men (MSM) (no consensus yet), *Chlamydia* and gonorrhea screen, syphilis testing, TST or IGRA, toxoplasma serology, CMV serology

NATURAL HISTORY OF HIV

VIRAL LOAD—rate of progression (speed of train). Indicates activity of viral replication. Critical measure of effect of antiretroviral therapy, once started
CD4 COUNT—progress and stage of disease (distance to crash). Indicates relative health of immune system and risk of opportunistic complication
FOLLOW-UP—viral load and CD4 count (usually 3–4-month intervals, or q2–8 weeks if change of HAART)
AIDS—CD4 < 200/mm^3 or any AIDS-defining diseases

- **BACTERIAL**—MAC, TB, recurrent *Salmonella* sepsis
- **VIRAL**—CMV retinitis, chronic HSV, PML
- **FUNGAL**—esophageal candidiasis, extrapulmonary coccidioidomycosis, histoplasmosis or cryptococcosis
- **PARASITIC**—*Pneumocystis jiroveci* pneumonia (PJP), toxoplasmosis, chronic Cryptosporidiosis or isosporiasis
- **HIV**—HIV encephalopathy, wasting syndrome
- **NEOPLASMS**—Kaposi's sarcoma, CNS lymphoma, non-Hodgkin's lymphoma, cervical carcinoma

MAJOR CAUSES OF DEATH IN HIV PATIENTS ON HAART—AIDS (30%), liver disease (14%), cardiovascular disease (9%), non-AIDS cancers (8%)

CD4 COUNT AND PATHOLOGIES IN HIV PATIENTS

CD4 count (/mm)^3	>500	200–500	100–200	<100
Kaposi sarcoma	+	+	+	+
Bacterial	+	+	+	+
TB	+	+	+	+
HSV	+	+	+	+
Candida		+	+	+
Coccidioides		+	+	+
Histoplasma		+	+	+
PJP			+	+
Cryptococcus				+
Toxoplasma				+
CMV				+
MAC				+
CNS lymphoma				+

CNS LESIONS IN HIV PATIENTS

DIFFERENTIAL DIAGNOSIS

- **BRAIN ABSCESS**—toxoplasma (CD4 < 100/mm^3, usually multiple ring-enhancing lesions), tuberculosis (any CD4), Cryptococcus (CD4 < 100/mm^3), Histoplasma (CD4 < 500/mm^3), aspergillosis
- **CNS LYMPHOMA** (CD4 < 100/mm^3)
- **PROGRESSIVE MULTI-FOCAL LEUKOENCEPHALOPATHY** (PML, CD4 < 100/mm^3)—reactivation of JC virus, hypodense white matter lesion

DIAGNOSIS—CBCD, lytes, urea, Cr, blood C&S, toxoplasma IgG antibodies, EBV PCR, JC virus PCR, CT/MR head, PET scan (CNS lymphoma has higher activity than abscess), brain biopsy (if suspect CNS lymphoma). The combination of (1) multiple ring enhancing lesions, (2) positive antitoxoplasmosis antibodies, and (3) lack of toxoplasma prophylaxis in a HIV patient with CD4 count <100/mm^3 has 90% PPV for diagnosing toxoplasma

TREATMENT OF TOXOPLASMOSIS—pyrimethamine plus either sulfadiazine or clindamycin

CHRONIC MENINGITIS IN HIV PATIENTS

DIFFERENTIAL DIAGNOSIS

- **CRYPTOCOCCUS** (CD4 < 100/mm^3)—ubiquitous fungus. High opening pressure (>200 cmH_2O)
- **BACTERIAL MENINGITIS** (any CD4)—*N. meningitis*, *S. pneumoniae*, *Listeria*, Gram-negative bacilli
- **VIRAL MENINGITIS** (any CD4)—HSV encephalitis

DIAGNOSIS—CBCD, lytes, urea, Cr, blood C&S, serum CRAG (sens 95% for Cryptococcus), CT head, lumbar puncture (for Cryptococcus and cryptoantigen)

TREATMENT OF CRYPTOCOCCUS—induction with *amphotericin B* 0.7 mg/kg IV daily plus *flucytosine* 25 mg/kg PO QID, switch to *fluconazole* 400 mg PO daily × 2 months for consolidation, followed by *fluconazole* 200 mg PO daily as maintenance. Management of increased intracranial pressure may be needed (neuroimaging to rule out concomitant space-occupying lesions, repeated LP to decrease ICP)

RESPIRATORY INFECTIONS IN HIV PATIENTS

DIFFERENTIAL DIAGNOSIS

- **COMMUNITY-ACQUIRED PNEUMONIA** (any CD4)—most common cause is *S. pneumoniae*. Others include *Moraxella*, *H. influenzae*
- **TUBERCULOSIS** (any CD4)—170× increased risk in HIV patients. May be extrapulmonary
- **NON-TB MYCOBACTERIUM**—MAC (CD4 < 100/mm^3, pulmonary involvement alone is rare, usually disseminated)

RESPIRATORY INFECTIONS IN HIV PATIENTS (CONT'D)

- **FUNGAL** (CD4 < 500/mm3)—*Histoplasma*, *Coccidioides*, *Cryptococcus*
- ***PNEUMOCYSTIS JIROVECII* PNEUMONIA** (PJP, CD4 < 200/mm^3)

DIAGNOSIS—CBCD, lytes, urea, Cr, LDH (↑ in PJP but non-specific), blood C&S and mycobacterial culture, sputum C&S and AFB, ABG (for PaO_2 and A-a gradient), urine C&S, CXR, bronchoscopy (lavage, biopsy)

TREATMENT OF PJP—*trimethoprim–sulfamethoxazole* 15 mg of TMP/kg PO/IV divided q8h daily × 21 days. If severe disease (PaO_2 ≤ 70 mmHg or A-a gradient ≥ 35 mmHg on room air), add *prednisone* 40 mg PO BID × 5 days, then 40 mg PO daily × 5 days, then 20 mg PO daily × 11 days. Alternatives to *trimethoprim–sulfamethoxazole* include dapsone plus trimethoprim, or clindamycin plus primaquine, pentamidine IV. Use atovaquone if G6PD deficiency

ESOPHAGITIS IN HIV PATIENTS

DIFFERENTIAL DIAGNOSIS

- **INFECTIONS**
  - **CANDIDA** (CD4 < 500/mm^3)—50–70%
  - **HSV** (any CD4)—5–10%
  - **CMV** (CD4 < 100/mm^3)—5–15%
- **NON-INFECTIOUS**—GERD, pill esophagitis, neoplasms
- **IDIOPATHIC** (any CD4)—10–30%

DIAGNOSIS—empiric therapy (fluconazole), endoscopy with cultures for fungus, virus, and biopsy

HEPATITIS/CHOLANGITIS/PANCREATITIS IN HIV PATIENTS

DIFFERENTIAL DIAGNOSIS

- **INFECTIONS**
  - **TB** (any CD4)
  - **MYCOBACTERIUM AVIUM COMPLEX** (MAC, CD4 < 100/mm^3)—*M. avium*, *M. intracellulare*
  - **VIRUSES**—HBV, HCV, CMV
  - **PARASITES**—Cryptosporidium, Microsporidium, Cyclospora
- **ALCOHOL**
- **DRUGS**—antiretrovirals, antibiotics (sulfa, isoniazid, rifampin, ketoconazole, fluconazole)

DIAGNOSIS—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, lipase, INR, cultures and serologies, US abd, CT abd, ERCP

COLITIS/DIARRHEA IN HIV PATIENTS

DIFFERENTIAL DIAGNOSIS

- **INFECTIONS**
  - **BACTERIAL**—*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, EHEC, EIEC, *C. difficile*
  - **TB** (any CD4)
  - **MYCOBACTERIUM AVIUM COMPLEX** (MAC, CD4 < 100/mm^3)—*M. avium*, *M. intracellulare*
  - **CMV** (CD4 < 100/mm^3)
  - **PARASITIC ★MAGIC★**—**M**icrosporidium, Ent**A**moeba, **G**iardia, **I**sospora, **C**ryptosporidium
- **MEDICATIONS**—antiretrovirals, antibiotics
- **AIDS ENTEROPATHY**—diagnosis of exclusion

DIAGNOSIS—CBCD, lytes, urea, Cr, stool C&S, stool O&P with acid fast staining, stool MAC, C. diff toxin, fecal WBC, Cryptosporidium, microsporidium

TREATMENT OF MAC—*clarithromycin* 500 mg PO BID or *azithromycin* 600 mg PO daily, plus *ethambutol* 15 mg/kg PO daily, plus *rifabutin* 600 mg PO daily for at least 12 months and at least 6 months of immune reconstitution (CD4 > 100–200/mm^3)

AIDS-ASSOCIATED MALIGNANCIES

AIDS-DEFINING MALIGNANCIES

- **KAPOSI'S SARCOMA** (any CD4)—strongly associated with HHV8. Lesions may involve skin, oral mucosa, lungs, and GI tract. Treat with liposomal doxorubicin. Lesions may also resolve with antiretroviral treatment
- **NON-HODGKIN'S LYMPHOMA** (CD4 < 100/mm^3)—diffuse large B-cell lymphoma, primary effusion lymphoma (associated with HHV8 and EBV), and plasmablastic lymphomas. Treat with combination chemotherapy (CHOPR)
- **PRIMARY CNS LYMPHOMA** (CD4 < 100/mm^3)—strongly associated with EBV. Treat with radiation and/or high-dose methotrexate or intrathecal chemotherapy
- **CERVICAL CARCINOMA** (any CD4)—strongly associated with HPV. Treat with surgery, radiation, and/or chemotherapy (cisplatin)

NON-AIDS-DEFINING MALIGNANCIES—increased incidence of Hodgkin's lymphoma, multiple myeloma, anogenital cancer, testicular cancer (seminoma), and basal cell carcinoma in HIV patients. Lung cancer, colorectal cancer, melanoma, squamous cell carcinoma of skin, and head and neck cancer may also be increased

EDUCATION, PROPHYLAXIS, AND IMMUNIZATION FOR HIV PATIENTS

EDUCATION AND COUNSELING—patient MUST be told to reveal HIV status to sexual partners (reportable disease). Advise regarding condom use and safer sex practices. Risk reduction strategies should be explored for substance abuse (e.g. avoid sharing needles or other drug paraphenalia), tobacco use, and other social issues. HIV is a chronic disease that can be successfully treated.

PJP PROPHYLAXIS—for patients with CD4 < 200/mm^3. *Trimethoprim–sulfamethoxazole* SS 1 tab PO daily, or *trimethoprim–sulfamethoxazole* DS 1 tab PO daily, or *trimethoprim–sulfamethoxazole* DS 1 tab PO three times a week. If allergic, desensitize or use dapsone or inhaled pentamidine

TOXOPLASMOSIS PROPHYLAXIS—for patients with positive *Toxoplasma* serology and CD4 < 100/mm^3. *Trimethoprim–sulfamethoxazole* DS 1 tab PO daily. If allergic, dapsone plus pyrimethamine plus folinic acid are alternatives

MAC PROPHYLAXIS—for patients with CD4 < 50/mm^3. *Azithromycin* 1200 mg PO once weekly

HISTOPLASMOSIS PROPHYLAXIS—for patients with CD4 < 150/mm^3 and living in endemic area. *Itraconazole* 200 mg PO daily

TB PROPHYLAXIS—for patients with positive TST reaction (induration ≥5 mm) and not treated for TB previously. *Isoniazid* 5 mg/kg/day PO daily to max 300 mg/day, or 900 mg thrice weekly × 9 months. *Rifampin* 600 mg PO daily × 4 month restricted to exposures to INH-resistant, RIF-susceptible isolates. Should be followed by a TB specialist

VACCINATIONS

- **GIVE**—Prevnar followed by pneumococcal polysaccharide vaccine at least 8 weeks later. Pnemococcal vaccine should be repeated every 5 years up to three doses. Hepatitis B vaccine (if non-immune), hepatitis A vaccine (if non-immune and especially if homosexual), influenza vaccine annually are all recommended
- **GENERALLY AVOID**—live vaccines (oral polio, varicella, measles-mumps-rubella, or yellow fever immunizations) if CD4 count is <200/mm^3

Related Topics
Hepatitis B (p. 145)
Hepatitis C (p. 147)
HIV in Pregnancy (p. 473)
Needle Stick Injury (p. 304)
Tuberculosis (p. 279)

ANTIRETROVIRAL THERAPY FOR HIV PATIENTS

NUCLEOSIDE AND NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTI)—zidovudine (ZDV, AZT), stavudine (d4T), didanosine (ddI), lamivudine (3TC), abacavir (ABC), tenofovir (TDF), and emtricitabine (FTC). Major side effects include hepatic steatosis, lactic acidosis, neuropathy, anemia, pancreatitis, and renal disease

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTI)—efavirenz (EFV), nevirapine (NVP), etravirine (ETR) and rilpivarine (RPV). Major side effects include rash, Stevens–Johnson syndrome, hepatitis, and CNS complications

PROTEASE INHIBITORS (PI)—saquinavir (SQV), indinavir (IDV), nelfinavir (NFV), lopinavir–ritonavir (LPV/RTV), fosamprenavir (FPV), atazanavir (ATV), tipranavir (TPV), and darunavir (DRV). Major side effects include hyperglycemia, fat redistribution syndrome, insulin resistance, and GI intolerance

INTEGRASE INHIBITORS—raltegravir, dolutegravir, elvitegravir

FUSION INHIBITOR (FI)—enfuvirtide (T-20)

CCR5 ANTAGONIST—maraviroc

EXAMPLES OF PREFERRED HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) REGIMENS

- NRTI (tenofovir plus emtricitabine) plus NNRTI (efavirenz)
- NRTI (tenofovir plus emtricitabine) plus PI (atazanavir/ritonavir or darunavir/ritonavir)
- NRTI (tenofovir plus emtricitabine) plus integrase inhibitor

THERAPEUTIC DECISIONS IN HIV

GOALS OF HIV THERAPY—durable suppression of HIV viral load to undetectable levels, reduction in HIV related morbidity, improvement in quality of life, prolongation of survival, restoration of immune function, and prevention of HIV transmission

APPROACH—start treatment in all symptomatic patients and in asymptomatic patients if CD4 < 500/mm^3. Treatment should be considered for all patients. Rapidly declining CD4 counts (>100/mm^3/year) or baseline viral loads >100,000 copies/mL increase the urgency of treatment. Initiate HIV treatment regardless of CD4 in pregnancy, HIV nephropathy, and in those with HBV when therapy for HBV is indicated. A commitment to lifelong treatment and adherence is essential prior to initiating therapy. HIV therapy is increasingly complex and should only be undertaken by those with expertise in HIV management

THERAPEUTIC DECISIONS IN HIV (CONT'D)

RESPONSE—successful if viral load ↓ by 2 logs after 8 weeks and ↓ to <50 copies/mL after 6 months of therapy. Need to continue therapy or may develop viral load rebound/drug resistance. If failure, consider non-adherence and/or resistance. Resistance testing should be performed, and the regimen should be changed based on resistance profile

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS) IN HIV PATIENTS

PATHOPHYSIOLOGY—delayed (1 week to several months) inflammatory response as the immune system is restored by antiretrovirals, leading to acute, paradoxical deterioration of pre-existing infections (TB, MAC, PJP, histoplasma, HCV, HBV). Clinical features highly variable. IRIS is a diagnosis of exclusion after considering drug reactions, non-adherence, new onset or progression of opportunistic infection. May occur in up to 25% of patients with opportunistic infections started on HAART (e.g. lymphadenopathy after starting antiretrovirals in patients with disseminated MAC or worsening CXR and fever in patients with TB). In general, treat opportunistic infections for 2 weeks prior to initiating antiretroviral therapy

TREATMENTS—supportive, continue antiretrovirals, give corticosteroids

VIRAL HEPATITIS IN HIV CO-INFECTED PATIENTS

HEPATITIS B

- **PATHOPHYSIOLOGY**—HIV/HBV co-infection rate is up to 20–30% in Asia/sub-Saharan Africa where transmission is mostly vertical or between young children and 5–10% in the USA and Europe where transmission is mostly via IDU and sexual contact. Co-infection is associated with increased risk of progression to end-stage liver disease
- **DIAGNOSIS**—for patients with isolated HBcAb, 10–45% have occult HBV infection with detectable levels of HBV DNA
- **PREVENTION**—hepatitis B vaccination of family and sexual partners
- **TREATMENT**—long-term combination therapy with a nucleoside analogue and nucleotide analogue (e.g. tenofovir plus either emtricitabine or lamivudine) is recommended in co-infected patients. Ultrasound and AFP recommended every 6 months for hepatocellular carcinoma screening

HEPATITIS C

- **PATHOPHYSIOLOGY**—HIV/HCV co-infection rate up to 70–95% for patients with IDU and hemo-

VIRAL HEPATITIS IN HIV CO-INFECTED PATIENTS (CONT'D)

philia and 1–12% for MSM. Coinfection results in more aggressive HCV, with more rapid progression to liver failure and hepatocellular carcinoma, particularly if concurrent alcohol use

- **DIAGNOSIS**—rarely may be HCV seronegative requiring PCR testing. Histologic injury as defined by liver biopsy or fibroscan is a much better predictor of clinical outcomes than liver enzymes or HCV viral load and may be useful in selected patients to guide therapy
- **PREVENTION**—risk reduction and safer needle use
- **TREATMENT**—for HCV is rapidly changing. New directly acting agents are replacing interferon and ribavirin as the drugs of choice for treatment of HCV with increased rates of cure and fewer side effects (see Chapter on Hepatitis C for more details. p. 290)

Influenza NEJM 2008 359:24

DIFFERENTIAL DIAGNOSIS

VIRAL—influenza A/B/C, parainfluenza, RSV, metapneumovirus, adenovirus, rhinovirus
BACTERIAL PNEUMONIA—*Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus*, *Moraxella*
ATYPICAL—*Mycoplasma*, *Chlamydia*, *Legionella*, TB, community-acquired MRSA

PATHOPHYSIOLOGY

CLASSIFICATION—the three types of influenza are A, B, and C. Influenza A can be classified into various subtypes based on the combination of two surface glycoproteins: neuraminidase (1 of 9 subtypes) and hemagglutinin (1 of 16 subtypes), e.g. H1N1, H1N2, and H3N2. Influenza A subtypes and influenza B can be further classified into various strains that arise due to antigenic drift
HOSTS—influenza B and influenza C viruses mainly affect humans. In contrast, influenza A can infect both humans and animals, including wild birds, poultry, pigs, dogs, and horses. Some influenza A strains are highly pathogenic and can cause severe disease in specific hosts, while others are associated with low pathogenicity. The process whereby at least two different viral strains combine to form a new subtype with a mixture of surface antigens of the original strains is termed antigenic shift and is the source of pandemic influenza virus

PATHOPHYSIOLOGY (CONT'D)

ANTIGENIC DRIFT—a gradual change in viral RNA sequence that occurs in both influenza A and B. This process is due to random point mutations in the genes encoding neuraminidase or hemagglutinin, creating strains of virus with new surface glycoproteins. Thus, antibodies against previous strains are ineffective. Can result in seasonal epidemics
ANTIGENIC SHIFT—an abrupt and significant emergence of novel viral strains. Only happens in influenza A. Antigenic shift occurs through mixing of human influenza A and animal (e.g. pig, bird) influenza A virus genes to create a new human influenza A subtype through a process called genetic reassortment (e.g. swine flu, avian flu). Rarely, avian strains of influenza may directly infect humans. Antigenic shift generates new virus and triggers pandemics as the majority of the population has no immunity against this new virus
PANDEMIC (worldwide outbreak)—based on the following criteria: (1) emergence of a new subtype of influenza A virus, (2) this virus is able to infect humans, (3) this virus can spread easily from person to person in a sustained manner

DISTINGUISHING FEATURES BETWEEN INFLUENZA A, B, AND C

	Influenza A	Influenza B	Influenza C
Hosts	Humans, Birds, Mammals	Humans only	Humans, Swine
Antigenic shift	Yes, creating new subtypes	No	No
Antigenic drift	Yes, creating new strains	Yes	Yes
Epidemics	Yes	Yes	No
Pandemics	Yes	No	No

CLINICAL FEATURES

SYMPTOMS—acute onset of systemic symptoms, such as fever, headache, myalgia, arthralgia, fatigue, and respiratory symptoms such as cough, dyspnea, and sore throat

CLINICAL FEATURES (CONT'D)

COMPLICATIONS—**respiratory** (bacterial pneumonia), **muscular** (rhabdomyolysis, myositis), **neurologic** (encephalitis, aseptic meningitis, transverse myelitis, Guillain–Barre syndrome)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE INFLUENZA?

	Sens (%)	Spc (%)	LR+	LR–
All age groups				
Fever	–	–	1.8	0.4
Feverishness	–	–	1.0	0.7
Cough	–	–	1.1	0.42
Myalgia	–	–	0.93	1.2
Malaise	73	26	0.98	1.1
Headache	–	–	1.0	0.75
Sore throat	–	–	1.0	0.96
Sneezing	–	–	1.2	0.87
Nasal congestion	–	–	1.1	0.49
Chills	83	25	1.1	0.68
Vaccine history	–	–	0.63	1.1
Fever and cough	64	67	1.9	0.54
Fever, cough, and acute onset	63	68	2.0	0.54
Rapid influenza testing	–	–	4.7	0.06
Age ≥60				
Fever	34	91	3.8	0.72
Feverishness	47	78	2.1	0.68
Cough	–	–	2.0	0.57
Myalgia	–	–	2.4	0.68
Malaise	57	78	2.6	0.55
Headache	–	–	1.9	0.70
Sore throat	–	–	1.4	0.77
Sneezing	32	33	0.47	2.1
Nasal congestion	47	50	0.95	1.0
Chills	46	82	2.6	0.66
Vaccine history	–	–	0.63	1.1
Fever and cough	30	94	5.0	0.75
Fever, cough, and acute onset	27	95	5.4	0.77

APPROACH—"clinical findings identify patients with influenza-like illness but are not particularly useful for confirming or excluding the diagnosis of influenza. Clinicians should use timely epidemiologic data to ascertain if influenza is circulating in their communities, then either treat patients with influenza-like illness empirically or obtain a rapid influenza test to assist with management decisions"

JAMA 2005 293:8

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, urinalysis
- **MICROBIOLOGY**—nasopharyngeal swab for rapid assays (variable sensitivity/specificity), RT-PCR (preferred), or DFA (direct fluorescent antigen detection). Blood C&S, sputum Gram stain/AFB/C&S, urine C&S
- **IMAGING**—CXR

SPECIAL

- **LUMBAR PUNCTURE**—if neurologic symptoms
- **ABG**

MANAGEMENT

PREVENTION IS KEY—annual vaccination for the following individuals: 50 or older, children 6–24 months or taking long-term salicylates, any chronic medical condition, pregnant women, healthcare workers, household contacts of those at risk, and residents of chronic care facilities. In some jurisdictions, universal vaccination for influenza is recommended. Depending on the match between vaccine and circulating virus, the efficacy can range from 70 to 90% for a good match and 0 to 50% for poor matches

TREATMENT—neuraminidase inhibitors (*oseltamivir* 75 mg PO BID × 5 days, or *zanamivir* 10 mg inhaled BID × 5 days) are active against influenza A and B. Antiviral treatment is most effective when started within 48 h of symptom onset. Treatment decreases the duration of symptoms by 1 day, reduces viral shedding, and may reduce complications in those at risk. Inhaled zanamivir is relatively contraindicated in patients with asthma or chronic respiratory conditions. Household contacts of infected individuals should be vaccinated and may be given prophylaxis with *oseltamivir* 75 mg PO daily or *zanamivir* 10 mg inhaled daily × 10 days. Resistance to oseltamivir is a problem in some strains of influenza A, and amantadine or rimantidine may have a role. Treatment of secondary bacterial pneumonia with antibiotics

CANDIDIASIS (CONT'D)

TREATMENT ISSUES

NEURAMINIDASE INHIBITORS—neuraminidase plays an important role for viral release from the host cell. Oral oseltamivir and inhaled zanamivir are active against both influenza A and influenza B

ADAMANTANES—block replication of influenza A RNA through inhibition of M2 protein ion channels. Amantadine and rimantadine are inactive against influenza B and C and resistance is now widspread in influenza A

VACCINE PRODUCTION—every February/March, the World Health Organization makes recommendations regarding the three strains (two A and one B) of influenza viruses that are most likely to cause outbreaks in the fall/winter in the upcoming season. Vaccines are then produced based on this decision

Antiviral Agents

Antiviral agents	Mechanism	HSV, VZV	CMV	Influenza A	Influenza B
Acyclovir 200–800 mg PO BID 5×/day; 5–10 mg/kg IV q8h	Nucleoside analogues—activated by viral thymidine kinase, inhibit viral DNA polymerase (vDNAp); also incorporated into viral DNA and act as a chain terminator	++			
Valacyclovir 500–1000 mg PO daily–TID		++			
Famciclovir 250–1000 mg PO BID		++			
Penciclovir 10 mg/g topically q2h × 4 days	Applied topically for treatment of oral cold sores	++			

Antiviral Agents (Cont'd)

Antiviral agents	Mechanism	HSV, VZV	CMV	Influenza A	Influenza B
Ganciclovir 5 mg/kg IV q12h or 1000 mg PO TID (maintenance)	Nucleoside analogue that inhibits viral DNA polymerase	++	++		
Valganciclovir 900 mg PO daily–BID		++	+++		
Foscarnet 90 mg/kg IV q12–24 h	Pyrophosphate analogue that inhibits viral DNA polymerase	++	+++		
Cidofovir 5 mg/kg IV q week	Nucleoside analogue that inhibits viral DNA polymerase	++	+++		
Amantadine 100 mg PO BID	Inhibit M2 Protein (ion channel) of influenza A, blocking uncoating of virus genome within newly infected cells			++	
Rimantadine 100 mg PO BID				++	
Zanamivir 10 mg INH q12–24 h	Neuraminidase Inhibitors. Block release of influenza virus from infected cells			++	++
Oseltamivir 75 mg PO daily–BID				++	++

Fungal Infections

GENERAL APPROACH

CLASSIFICATION—fungal infections can be classified into three main categories: yeasts, molds ("filamentous fungi"), and dimorphic fungi

- **YEASTS**—grow as single cells (via budding) and include *Candida*, *Malassezia*, *Rodotorula*, *Trichosporon*
- **MOLDS**—these filamentous fungi grow as hyphae (via sexual and asexual reproduction) and include *Aspergillus*, zygomycetes, *Fusarium*, and dematiaceous (pigmented) fungi. Ubiquitous in the environment (e.g. soil, decaying vegetation, water, air). Infection may cause blood vessel invasion, thrombosis, and obstruction. Clinical syndromes include cerebral parenchymal infections, pulmonary parenchymal infections, hepatosplenic abscesses, and otitis externa

GENERAL APPROACH (CONT'D)

GENERAL APPROACH (CONT'D)

- **DIMORPHIC FUNGI**—exist as both molds and yeasts and include *Coccidioides*, *Histoplasma*, *Blastomyces*, and *Cryptococcus*. At low temperatures, found as multicellular molds (which release spores that are inhaled). In warm temperatures (e.g. inside the body), inhaled spores germinate into yeasts, which are infectious to the patient, but no longer contagious (i.e. these patients do not require isolation)

CANDIDIASIS

PATHOPHYSIOLOGY—*Candida albicans* ("Germ-tube positive" with pseudohyphae) or non-albicans species ("Germ-tube negative," e.g. *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*), mostly in patients with hematological malignancy, neutropenia, on immunosuppressants, IDU, or those in the intensive care unit with hemodialysis, broad-spectrum antibiotics, surgery, central venous catheters, and parenteral nutrition

CLINICAL FEATURES—localized mucocutaneous infections (thrush and vaginitis), serious focal infections (endophthalmitis, meningitis, osteomyelitis), or disseminated infection (candidemia) with pustular skin lesions, retinal lesions. Candiduria is common in ICU patients, but usually represents colonization unless patient is symptomatic

TREATMENTS

- **OROPHARYNGEAL**—*clotrimazole troche* 10 mg 5× daily, *nystatin* suspension (500,000 U) or *nystatin pastilles* (200,000 U) 4× daily, *fluconazole* 100 mg PO/IV daily × 1–2 weeks
- **ESOPHAGITIS**—*fluconazole* 400 mg loading dose, then 200 mg PO/IV daily × 2–3 weeks
- **CANDIDURIA**—remove catheter, indications for treatment include kidney transplant recipients, prior to cystoscopy or invasive GU procedure, neonates, severe illness, and possibly neutropenia (controversial). *Fluconazole* 200 mg PO/IV daily × 2 weeks
- **ACUTE DISSEMINATED CANDIDEMIA**—remove all intravascular devices. *Fluconazole* 800 mg IV loading dose, then 400 mg PO/IV daily × 2 weeks (minimum), or one of the echinocandins, including *caspofungin* 70 mg then 50 mg IV daily, *micafungin* 100 mg IV daily, or *anidulafungin* 200 mg loading, then 100 mg IV daily × 2 weeks (minimum) after last positive culture for *C. albicans*. Echinocandin and lipid formulation of amphotericin B are preferred for initial therapy in neutropenic patients. Almost all (>95%) *C. albicans* are sensitive to fluconazole. Some laboratories report *C. albicans* as "*C. albicans complex*" because of structural resemblance between *albicans* and *dubliniensis*. This is of no clinical significance because *albicans* and *dubliniensis* have the same susceptibility patterns. Susceptibility patterns for other non-albicans infections may significantly differ. Consider echinocandin for non-albicans Candidiasis

CID 2009 48:5

CANDIDIASIS (CONT'D)

ASPERGILLOSIS

MICROBIOLOGY—genus contains >185 species including *A. fumigatus* (80% of clinical infections), *A. flavus*, *A. niger*, *and A. terreus*

PATHOPHYSIOLOGY—mostly in patients with neutropenia, organ or stem cell transplants, advanced AIDS, or on corticosteroids. Invasive aspergillosis has mortality of >50%

CLINICAL FEATURES—spectrum of pulmonary involvement includes colonization, pulmonary aspergilloma ("fungal ball"), allergic bronchopulmonary aspergillosis (ABPA), chronic necrotizing aspergillus pneumonia (CNPA), and invasive aspergillosis. Second most common cause of fungal endocarditis (after *Candida*). Cutaneous involvement may follow trauma or dissemination from respiratory tract

DIAGNOSIS—often difficult and may require biopsy with culture and histology. Check quantitative immunoglobulin, aspergillus IgG and IgE, galactomannan levels (suggestive of invasive aspergillosis). CT chest may show multiple nodular lesions (halo sign = nodule with surrounding hemorrhage, air crescent sign = necrosis and cavitation). Sputum fungal culture and eosinophils, bronchoalveolar lavage, or lung biopsy. The galactomannan assay is relatively specific for invasive aspergillosis, and, in the right clinical context, provides adequate evidence of invasive pulmonary disease. This assay can be done on serum or BAL specimens

TREATMENTS—*voriconazole* 6 mg/kg q12h × 24 h then 4 mg/kg IV q12h or 200 mg PO BID until resolved. Alternatives include *caspofungin* 70 mg then 50 mg IV q24h, lipid-formulation *amphotericin B* 3–5 mg/kg IV daily, *micafungin* 100–150 mg IV daily, *posaconazole* 200 mg PO QID then 400 mg BID after clinical stabilization. Some species, especially *A. terreus*, are resistant to amphotericin. *Aspergillus* is the only filamentous fungus that can be treated with echinocandins

CID 2008 46:3
Clin Infect Dis. 2009 49:11
J Clin Microbiol. 2010 48:4

ZYGOMYCETES (MUCORMYCOSIS)

MICROBIOLOGY—large group of filamentous fungi including *Rhizopus*, *Absidia*, *Rhizomucor*, *Mucor*, and *Cunninghamella*

PATHOPHYSIOLOGY—mostly affecting immunocompromised patients and those with diabetes. Prognosis extremely poor

CLINICAL FEATURES—CNS, pulmonary, GI, and cutaneous involvement. Infection can cause devastating rhino-orbital-cerebral and pulmonary infections

TREATMENTS—antifungal therapy frequently needs to be combined with surgical debridement. Empiric treatment options include lipid formulations of amphotericin B and pozaconazole. Note that susceptibility testing of Zygomycetes is not always reliable, and that caspofungin and "azoles" (apart from pozaconazole) are not generally effective

HISTOPLASMOSIS

PATHOPHYSIOLOGY—*H. capsulatum* endemic along St. Lawrence seaway and in Midwestern states located along the Ohio and Mississippi River valleys. Symptoms typically occur in patients who are immunocompromised or exposed to a large inoculum

CLINICAL FEATURES—usually asymptomatic. Pulmonary manifestations may mimic sarcoidosis and include pneumonia (localized or diffuse), granuloma/cavitary lung lesions, and hilar and mediastinal lymphadenopathy. Pericarditis, arthritis, arthralgia and erythema nodosum may also occur without pulmonary symptoms. Disseminated disease may present with hepatosplenomegaly, pancytopenia, oropharyngeal ulcers, skin, and CNS involvement

DIAGNOSIS—fungal culture of blood and tissue, urine antigen, *Histoplasma* serology, and histopathology. *Histoplasma* is predominantly an intracellular pathogen; therefore cultures need to be placed in "isolator tube" (containing cell lysis product)

TREATMENTS—*itraconazole* 200 mg PO TID × 3 days, then 200 mg PO daily–BID, lipid formulation of amphotericin B (preferred for ill patients)

CID 2007 45:7

CRYPTOCOCCOSIS

MICROBIOLOGY—formerly believed to be unicellular yeast, although now confirmed to be dimorphic. Unlike other dimorphic fungi (e.g. *Histoplasma*, *Blastomyces*, *and Coccidioides*), *Cryptococcus* is ubiquitous and not geographically isolated. *Cryptococcus neoformans* has two varieties: *C. neoformans* var. *neoformans* and var. *gattii*

PATHOPHYSIOLOGY

- ***C. NEOFORMANS***—almost invariably in immunocompromised patients including HIV with CD4 < 100/mm^3, transplantation, hematologic malignancies, chronic kidney diseases, diabetes mellitus, cirrhosis, or corticosteroid use. This pathogen is inhaled, then disseminates with predilection for CNS with meningitis more common than focal parenchymal infections
- ***C. GATTII***—seen more commonly in immunocompetent hosts and paradoxically uncommon in immunosuppressed hosts. Symptomatic infection is usually pulmonary ± focal parenchymal brain infection

CLINICAL FEATURES—CNS, pulmonary, and cutaneous involvement (but may involve any organ)

TREATMENTS—**CNS infection** (lumbar puncture to lower intracranial pressure, amphotericin B plus flucytosine, followed by fluconazole), **pulmonary or cutaneous infection** (fluconazole or itraconazole)

CID 2010 50:3

COCCIDIOIDOMYCOSIS

PATHOPHYSIOLOGY—endemic to lower deserts of southern Arizona, central California, southwestern New Mexico, and west Texas in USA. Also Mexico, Central and South America. Peak incidence from May–July and October–December. Affects mostly patients with immunosuppression

CLINICAL FEATURES—an acute pulmonary infection that is often asymptomatic, but can cause a flu-like illness or pneumonia. Pulmonary symptoms include chest pain, cough, fever, and hemoptysis if cavitary lesions. Radiologically, unilateral infiltrate and hilar adenopathy are common. Cutaneous symptoms include erythema nodosum and erythema multiforme. Most common sites of dissemination are skin, bone, and meninges

COCCIDIOIDOMYCOSIS (CONT'D)

DIAGNOSIS—fungal culture and serology. Note that *Cocciodioides* is a level 3 pathogen. Therefore, cultures should be processed in high-level isolation unit and labeled carefully. There have been numerous reports of iatrogenic infection of laboratory personnel when adequate precautions not taken

TREATMENTS—usually resolves spontaneously if uncomplicated disease. Antifungal therapy may need to be combined with surgery for certain pulmonary infections. *Fluconazole* 400 mg PO daily, *itraconazole* 200 mg PO daily (duration dependent on site of infection and may last months to years). *Coccidioides* meningitis should be treated with amphotericin B

CID 2005 41:9

BLASTOMYCES

PATHOPHYSIOLOGY—mostly found in northwest Ontario, the Great Lakes, and some Eastern states (e.g. Ohio, Mississippi River valley). Infection occurs by inhalation of aerosolized spores from soil

CLINICAL FEATURES—asymptomatic infection is common. Pulmonary symptoms of acute or chronic pneumonia (incubation time 45–100 days). Extrapulmonary dissemination to skin, bone/joint, GU tract, usually associated with pulmonary disease

DIAGNOSIS—fungal culture. Presence of "broad-based budding yeast" in clinical specimens strongly suggests *Blastomyces*

TREATMENTS—amphotericin B or lipid formulation for moderate to severe disease or CNS involvement. Itraconazole for mild disease or step-down but has poor blood–brain barrier penetration; alternatives are voriconazole or fluconazole

CID 2008 46:12

INDICATIONS FOR VORICONAZOLE

INVASIVE ASPERGILLOSIS—first line treatment for invasive and CNS

INVASIVE CANDIDIASIS—second or third line treatment for patients who are refractory or intolerant of fluconazole (first line for some).

FUNGEMIA—empiric treatment for fungi not yet speciated where neither amphotericin B nor fluconazole can be used

FEBRILE NEUTROPENIA—empiric antifungal treatment for patients with suspected aspergillus infection

INDICATIONS FOR CASPOFUNGIN/MICAFUNGIN

INVASIVE ASPERGILLOSIS—third line treatment for patients who are refractory or intolerant of voriconazole (first line) or amphotericin B (second line)

INVASIVE CANDIDIASIS—second line treatment for patients who are refractory or intolerant of fluconazole (first line for some)

FUNGEMIA—empiric treatment for fungi not yet speciated where neither amphotericin B nor fluconazole can be used

FEBRILE NEUTROPENIA—empiric antifungal treatment

TREATMENT DEFINITIONS

REFRACTORY—persistence of positive cultures OR lack of clinical response despite ≥5 days of therapy and removal of catheter if applicable

INTOLERANCE—serum creatinine doubling from baseline AND ≥450 μmol/L [≥5.1 mg/dL], tripling of serum creatinine from baseline, creatinine clearance ≤40 mL/min or concomitant administration of nephrotoxins, documented allergy, or intolerable infusion reactions

Antifungal Agents

	Mechanism	Candida	Cryptococcus	Aspergillus	Other molds[a]	Dimorphic[b]	Zygomycota[c]	Renal adjustments
Azoles								
Fluconazole[d] 100–400 mg PO/IV daily	Inhibits CP450 (convert lanosterol to ergosterol on cell membrane)	++C. alb	+++			+		Yes (dose)
Itraconazole[e] 100–200 mg PO daily–BID		+++		++	++	++		No
Voriconazole[f] 4 mg/kg IV q12h or 200 mg PO BID		+++		+++	++Fusa/ Scedo	++		No but avoid IV form
Posaconazole 200 mg PO QID		+++	+++	+++	+++Fusa	++	+++	No
Amphotericin B[g]								
Amphotericin B 0.3–1 mg/kg IV q24h	Binds to ergosterol on cell wall, causing cell leakage	+++	+++	++	+	+++	+++	Yes (interval)
Liposomal AmphoB 3–5 mg/kg IV q24h		+++	+++	++	+	+++	+++	Yes (interval)
AmphoB colloidal dispersion		+++	+++	++	+	+++	+++	Yes (interval)
AmphoB lipid complex 5 mg/kg IV q24h		+++	+++	++	+	+++	+++	Yes (interval)
Echinocandin[h]								
Caspofungin 70 mg then 50 mg IV q24h	Inhibits synthesis of β-1,3-d-glucan on cell wall	+++		+++	+Scedo	+/–		No

Antifungal Agents (Cont'd)

	Mechanism	Candida	Cryptococcus	Aspergillus	Other molds[a]	Dimorphic[b]	Zygomycota[c]	Renal adjustments
Micafungin 150 mg IV q24h		+++		+++				No
Anidulafungin 200 mg then 100 mg IV q24h		+++		+++				No
5-Flucytosine 5 Flucytosine	Inhibits synthesis of DNA (thymidylate synthetase)	+++	+++				++	Yes (dose)

[a]other than *Aspergillus*, *Fusarium*, *Scedosporium*, and *Pseudallescheria boydii* are all examples of molds
[b]dimorphic fungi include *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, and *Sporothrix schenckii*
[c]zygomycota fungi include *Rhizopus*, *Mucor*, and *Absidia*
[d]fluconazole is ineffective against some *Candida*, molds, and *Zygomycetes*
[e]itraconazole is ineffective against some *Candida*, *Scedosporium*, and *Zygomycetes*. It has activity against *Cryptococcus*, but has less CSF penetration than fluconazole
[f]voriconazole is ineffective against some *Candida*, *Scedosporium*, and *Zygomycetes*. It has activity against *Cryptococcus*, but has less CSF penetration than fluconazole
[g]amphotericin B is ineffective against molds (*Fusarium*, *Scedosporium*, *Trichosporum*, *Aspergillus terreus*), *C. guilliermondii* and *C. lusitaniae*
[h]caspofungin is ineffective against *Zygomycetes*, *Cryptococcus*, and *Fusarium* but probably has activity against other molds

Infection Control

NOSOCOMIAL INFECTIONS

DEFINITION—infections acquired in hospital that occur between 48 and 72 h after admission and up to 72 h after discharge (up to 30 days for surgical procedures)

URINARY TRACT INFECTIONS—secondary to urinary catheters. Infection rates are 1–5%, up to 100% for long-term catheterization. Complications include cystitis, prostatitis, pyelonephritis, and urosepsis

VENTILATOR-ASSOCIATED PNEUMONIAS—secondary to mechanical ventilation (after >48 h, p. 105)

BACTEREMIA—secondary to central venous catheters. Infection rates are 3–7%

SURGICAL SITE INFECTIONS—secondary to incisions

PREVENTION STRATEGIES—hand washing, hand washing, and hand washing! Education, isolation, and surveillance are important. Practice routine/standard/universal precautions with the use of gloves when handling all body fluids except sweat. Always use sterile technique when inserting urinary and central venous catheters. Minimize NG tube insertion and keep patient head of bed 30–45° if intubated

ISOLATION

- **AIRBORNE** (negative pressure room with high-efficiency particulate aerator filter, certified N95 respirator for personal protection)—varicella, tuberculosis, measles. Negative pressure room required
- **DROPLET** (mask within 3–6 ft; eye protection)—*H. influenzae*, *N. meningitidis*, influenza, RSV, pertussis, parainfluenza, adenovirus, human metapneumovirus and other respiratory viruses
- **CONTACT** (glove, gown, wash hands)—*C. difficile*, VRE, MRSA, carbapenem-resistant organism (CRO), ESBL

***N. MENINGITIDIS* PROPHYLAXIS**

- **CHEMOPROPHYLAXIS**—for exposures in last 7 days with *ciprofloxacin* 500 mg PO×1 dose or *rifampin* 600 mg PO BID×2 days can be used to reduce the risk of *N. meningitidis* in "close contacts." Vaccines are not recommended for primary prophylaxis post-exposure, but may be useful for epidemic control on a population basis
- **CLOSE CONTACTS**—defined as healthcare workers with direct exposure to respiratory secretions (e.g. mouth-to-mouth resuscitation or intubation), household members, intimate contacts, children in school environments, coworkers in the same office, young adults in dormitories, and recruits in training centers. Not recommended for most medical personnel (i.e. those without direct exposure to patient's oral secretions) or for casual or indirect contacts (e.g. school or workmates)

NEEDLE STICK INJURY

PREVENTION—routine/standard/universal precautions (gloves, gowns, masks if risk of exposure of body fluids), never recap needles, education

PRE-EXPOSURE PROPHYLAXIS—immunization (hepatitis B vaccine at 0, 1, 6 months)

RISK OF TRANSMISSION—depends on the mechanism of exposure, source patient characteristics, pre and post-exposure prophylaxis

- **HBV**—6–30% if source positive. Transmission via urine, feces, and saliva unlikely
- **HCV**—1.8% if source positive. Transmission via urine and feces unlikely
- **HIV**—0.3% if source positive. Transmission via urine, feces, and saliva unlikely

POST-EXPOSURE PROCEDURE

- **SOURCE PATIENT TESTING**—HBV, HCV, HIV
- **EXPOSED PERSON BASELINE TESTING**—HBV, HCV, HIV (ELISA, Western), CBCD, lytes, urea, Cr, AST, ALT, ALP, bili
- **HBV PROPHYLAXIS**—HB Ig (only if source patient is HBsAg positive or unknown and the exposed person is unvaccinated) and start vaccination for HBV
- **HIV PROPHYLAXIS**—antiretroviral therapy for 30 days (if source patient HIV positive or source patient unknown and high risk). Therapy may include raltegravir and truvada (tenofovir/emtricitabine). If source patient ARV resistance testing known, post-exposure procedure can be tailored accordingly. Treatment should be started within 4 h
- **COUNSELING**—protective sexual intercourse, hold blood donation and breastfeeding, side effects of prophylactic medication(s), follow-up in 2 weeks

http://www.health.alberta.ca/documents/PEP-Guidelines-2013.pdf

PROPHYLAXIS FOR OTHER INFECTIOUS AGENTS— diphtheria (penicillin or erythromycin), pertussis (trimethoprim–sulfa, erythromycin), rabies (rabies immune globulin, vaccine), varicella zoster (varicellazoster immune globulin, vaccine), hepatitis A (immune globulin, vaccine)

Immunization for Adults

http://www.phac-aspc.gc.ca/publicat/cig-gci/p03-02-eng.php

Vaccine	Type	Schedule	Indications	Contraindications
Viral vaccines				
Measles SC	Live	0, +1 months (if high risk)	All adults not previously immunized in childhood	Preg, immunocomp.
Mumps SC	Live	0, +1 months (if high risk)	All adults not previously immunized in childhood	Preg, immunocomp.
Rubella SC	Live	0, +1 months (if high risk)	All adults not previously immunized in childhood	Preg, immunocomp.
Polio IM/SC	Inactivated	–	Not routinely recommended for adults	–
HBV IM	Recombinant	0, +1 months, +6 months	All adults not previously immunized in childhood, particularly high-risk groups for parenteral or sexual exposure, chronic liver disease (e.g. chronic HCV/HBV), chronic renal disease, healthcare workers, MSM, household and sexual contacts of those with chronic HBV, those with or evaluated for STDs	–
HAV IM	Inactivated	0, +6 months	Travelers (esp. developing world), chronic liver disease (e.g. chronic HCV/HBV), MSM, ?food handlers	–
Influenza IM	Inactivated	Annually (Oct)	Adults >50 year, >6 month-50 years with chronic disease, pregnancy, healthcare workers	
Varicella SC	Live	0, 1–2 months	All who have not had chicken pox by adulthood, especially healthcare workers	Preg, immunocomp.
Herpes zoster SC	Live	1 dose	Adults >60 years. Note this vaccine has higher dose of attenuated virus than varicella vaccine	Preg, immunocomp, no history of Varicella
HPV IM	Recombinant	0, +1–2 months, +6 months	Females aged 9–26 years (licensed also for males in some countries) Controversial as outcomes data pending	–

Immunization for Adults (Cont'd)

Vaccine	Type	Schedule	Indications	Contraindications
Bacterial vaccines				
Pertussis	Cellular	1 dose	All adults not previously immunized in childhood; single dose of acellular Pertussis vaccine combined with Tetanus/diphtheria (Tdap) recommended for adults aged 19–64	–
Td (tetanus, diphtheria) IM	Toxoid, inactivated	0, +2 months, +6–12 months, q10 year	All adults not previously immunized in childhood (see Tdap under Pertussis)	–
Pneumococcal IM/SC	Polysaccharide	0, +5 year	Adults >65 years, >6 months–50 years with chronic disease, pregnancy, splenectomy, malignancy, smokers	–
Haemophilus type B	Conjugated	1 dose	Splenectomy	–
Meningococcal SC	Polysaccharide	1 dose	Splenectomy, college dormitory students, lab workers, travelers to endemic areas	–

PRINCIPLES

RISK FACTORS FOR SPECIFIC ORGANISMS

- **HBV**—household contacts/sexual partners of hepatitis patients, IDU, homosexual, multiple sexual partners, tattoo, piercing, transfusions, healthcare workers (prior to vaccine era), residents/workers of institutions for mentally ill or criminals, birth in endemic country
- **HCV**—sexual partners (controversial), IDU, tattoo, piercing, transfusions, residents/workers of institutions for mentally ill or criminals

PRINCIPLES (CONT'D)

- **PNEUMOCOCCAL**, **MENINGOCOCCAL**, **HAEMOPHILUS INFLUENZAE**—splenectomy

CONTRAINDICATIONS

- **ALL VACCINES**—anaphylaxis, severe illness
- **LIVE VACCINES**—pregnancy, immunocompromised (steroids, AIDS but not HIV, malignancies)

SIDE EFFECTS—local erythema, fever

9
RHEUMATOLOGY

Steven J. Katz

Septic Arthritis

DIFFERENTIAL DIAGNOSIS OF MONOARTHRITIS

★ICU RN★

INFECTIONS

- **BACTERIAL**—Gonococci, *Staphylococcus aureus*, *Streptococcus*, Enterobacteriaceae, *Borrelia burgdorferi*, Syphilis, TB
- **VIRAL**—HIV, HBV, Parvovirus, rubella, mumps, enterovirus, adenovirus
- **FUNGAL**—*Cryptococcus*, *Blastococcus*
- **OSTEOMYELITIS/OSTEONECROSIS EXTENDING TO JOINT**

CRYSTAL—**gout**, **pseudogout**, **hydroxyapatite**, **basic calcium phosphate**

UNCLASSIFIED

- **TRAUMA**
- **OSTEOARTHRITIS**
- **HEMARTHROSIS**—coagulopathy, thrombocytopenia, pigmented villonodular synovitis, trauma
- **NON-ARTHRITIS**
  - **BONE**—osteomyelitis, avascular necrosis, fracture
  - **SOFT TISSUE**—tendonitis, ligament tear, bursitis, myositis, meniscus tear

RHEUMATOLOGIC (**early stage**, **unusual presentation as monoarthritis**)

- **SEROPOSITIVE★PSSR★**—**P**olymyositis, **P**alindromic rheumatism, **S**LE, **S**cleroderma, **R**heumatoid arthritis
- **SERONEGATIVE★PEAR★**—**P**soriatic arthritis, **E**nteric arthritis, **A**nkylosing spondylitis, **R**eactive arthritis
- **SARCOIDOSIS**, **POLYMYALGIA RHEUMATICA**

NEOPLASTIC—chondrosarcoma, osteoid osteoma, metastasis

PATHOPHYSIOLOGY

RISK FACTORS—50% of sexually active adults with septic arthritis are due to gonococcal infections, while most patients with risk factors for septic arthritis listed below are due to non-gonococcal infections (*S. aureus*, Streptococci, Gram-negative bacilli)

PATHOPHYSIOLOGY (CONT'D)

- **COMORBIDITIES**—diabetes, chronic kidney disease, rheumatologic disease, cancer, advanced disability
- **TREATMENT RELATED**—immunosuppressive therapy (glucocorticoids, cytotoxic agents), prosthetic joint
- **SPECIFICS**—IDU (more axial joints with MRSA, Gram negative especially *Pseudomonas*), endocarditis (sterile fluid as autoimmune process)

GONOCOCCAL ARTHRITIS—more common in women. Less destructive and has better outcome than non-gonococcal arthritis. The synovial fluid Gram stain is only positive in <10%, and culture is often negative in gonococcal arthritis

COMPLICATIONS—osteomyelitis (30%), permanent joint damage, sepsis

CLINICAL FEATURES

HISTORY—arthritis (location, duration, pain, range of motion, function), adenopathy, fever, rash, oral ulcers, alopecia, Raynaud's, photosensitivity, sicca, trauma, recent infections, cervical/urethral discharge, sexual encounters, diarrhea, recent travel, past medical history (pre-existing joint disease, gout, rheumatoid arthritis, SLE, IBD, psoriasis, diabetes, IDU), medications (anticoagulants)

PHYSICAL—vitals (fever), joint examination (tenderness, swelling, range of motion). Look for nail pitting, onycholysis, tophi, rheumatoid nodules, track marks, psoriasis, keratoconjunctivitis sicca, uveitis, conjunctivitis, episcleritis, murmurs, urethral discharge, and penile ulcers. Examine all joints and pay particular attention to the affected one. Soft tissue injuries (bursitis, tendonitis, muscles) usually have decreased active range of motion but normal passive range of motion, while

D. Hui et al. (eds.), *Approach to Internal Medicine: A Resource Book for Clinical Practice*,
DOI 10.1007/978-3-319-11821-5_9, © Springer International Publishing Switzerland 2016

CLINICAL FEATURES (CONT'D)

both active and passive range of motion would be affected in joint diseases. Pelvic examination to inspect the cervix and to look for pelvic inflammatory disease

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS ADULT PATIENT HAVE SEPTIC ARTHRITIS?

	Sens (%)	Spc (%)	LR+	LR–
History				
Age >80	19	95	3.5	0.86
Diabetes	12	96	2.7	0.93
Rheumatoid arthritis	68	73	2.5	0.45
Recent joint surgery	24	96	6.9	0.78
Hip/knee prosthesis	35	89	3.1	
Skin infection	32	88	2.8	0.73
HIV infection	79	50	1.7	0.47
Joint pain	85			
Joint edema	78			
Fever	57			
Sweats	27			
Rigors	19			
Physical				
Fever	46	31	0.67	1.7
Investigations				
Elevated WBC	90	36	1.4	0.28
Elevated ESR	95	29	1.3	0.17
Elevated CRP	77	53	1.6	0.44
Synovial fluid analysis				
WBC >100,000/mL	29	99	28	0.71
WBC >50,000/mL	62	92	7.7	0.42
WBC >25,000/mL	77	73	2.9	0.32
PMN ≥90%	73	79	3.4	0.34

APPROACH—"when evaluating a patient with a painful, peripheral, swollen joint, the underlying pathology of a monoarthritis may be difficult to diagnose by clinical history and examination alone due to nonspecific symptoms and signs. Identifiable risk factors and arthrocentesis are most helpful in predicting septic arthritis. In particular, synovial WBC count and percentage of polymorphonuclear cells provide the best utility in identifying septic arthritis while waiting for Gram stain and culture test results. There is no evidence that a patient's symptoms or the physical examination are useful for predicting non-gonococcal bacterial arthritis"

JAMA 2007 297:13

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, uric acid, ANA, RF, ESR, CRP, INR, PTT
- **IMAGING**—joint XR (chondrocalcinosis in pseudogout; the presence of crystals does not rule out sepsis)
- **ARTHROCENTESIS**—★**3C**★ (**C**ell count with diff, **C**ulture and Gram stain, **C**rystals)

SPECIAL

- **INFECTIOUS WORKUP**—urethral/rectal swabs, blood C&S

DIAGNOSTIC ISSUES

GOLDEN RULE—patients with monoarthritis have septic arthritis until proven otherwise. Joint infection is a rheumatologic emergency as permanent damage can occur. Presence of crystal does not rule out infection. In up to 75% of patients with septic arthritis, a focus of infection may be found

ARTHROCENTESIS FLUID ANALYSIS

	Normal	Non-Infectious	Infectious	Septic
WBC (/mm^3)	<200	200–2000	2000–50,000	>50,000
PMNs	<25%	<25%	25–50%	>50%

JOINT ASPIRATIONS/INJECTIONS—for diagnostic and sometimes therapeutic reasons. Absolute contraindication is infection overlying site of injection. Relative contraindications include *significant* hemostasis defects and bacteremia (**NEJM 2006 354:e19**)

- **KNEE**—flex 10–15°, enter either medially or laterally immediately beneath the undersurface of the patella slightly above midway
- **ANKLE**—foot perpendicular to leg, medial approach immediately medial to the extensor hallucis longus tendon. Lateral approach just distal to fibula
- **WRISTS**—flex slightly. Medial approach at dorsal surface between the distal ulna and the carpal bones. Lateral approach at dorsum just distal to the end of the radius, between the extensor tendons of the thumb
- **ADVERSE EFFECTS OF ASPIRATIONS/INJECTIONS**—hypersensitivity to anesthetic, pain, infection, tendon rupture, subcutaneous atrophy, post-injection flare, systemic steroid absorption, hemorrhage, steroid arthropathy

MANAGEMENT

REMEMBER TO ALWAYS ASPIRATE BEFORE PROCEEDING TO TREATMENT

SYMPTOM CONTROL—NSAIDs/opioids for pain

TREAT UNDERLYING CAUSE—**empiric** (if not at risk for sexually transmitted disease, *nafcillin* 2 g IV q4h or *vancomycin* 1 g IV q12h, plus *ceftriaxone* 2 g IV q24h or *cefotaxime* 2 g IV q8h. If at risk of sexually transmitted disease, *nafcillin* 2 g IV q4h for Gram positive organisms on Gram stain; otherwise, give *ceftriaxone* 2 g IV q24h or *cefotaxime* 2 g IV q8h if organisms not identifiable yet). **Gonococcal** (*ceftriaxone* 1 g IV q24h). **Lyme arthritis** (*amoxicillin* 500 mg PO TID, *doxycycline* 100 mg PO BID, or *ceftriaxone* 2 g IV daily × 4 weeks). **Therapeutic arthrocentesis. Arthroscopic or surgical drainage** (if joint inaccessible to needle drainage, organism resistant to antibiotics, or no clinical response in 3–4 days)

Gout NEJM 2003 349:17

CAUSES

DECREASED URATE EXCRETION (90%)

- **RENAL DISEASE**
- **DRUGS ★CAN'T LEAP★**—**C**yclosporine, **A**lcohol, **N**icotinic Acid, **T**hiazides, **L**oop diuretics, **E**thambutol, **A**SA (low dose), **P**yrazinamide

INCREASED URATE PRODUCTION (10%)

- **METABOLIC SYNDROME**—obesity, hyperlipidemia, hypertension
- **INCREASED METABOLISM**—alcohol, hemolytic anemia, psoriasis, Lesch–Nyhan syndrome
- **NEOPLASTIC**—myeloproliferative disease, lymphoproliferative disease, chemotherapy

PATHOPHYSIOLOGY

IMBALANCE—decreased urate excretion and/or increased urate production → uric acid crystals deposited in joints, skin, and kidneys → arthritis, tophi, and renal failure. Gout almost never occurs in pre-menopausal women (estrogen promotes higher urinary fractional excretion of urate)

PRECIPITANTS—surgery, dehydration, fasting, binge eating, binge drinking, exercise, trauma

CLINICAL FEATURES

SYMPTOMS

- **ARTHRITIS**—mono/oligo and asymmetric, especially first MTP joint. Podagra, inflammation of the first MTP joint, is the presenting symptom in 75% of gout patients. However, the first MTP is also commonly affected in pseudogout, psoriatic arthritis, sarcoidosis, osteoarthritis, and trauma
- **TOPHI**—yellowish-white nodular urate crystals collection in subcutaneous tissues (particularly colder extremities such as ear, fingers, olecranon bursa, ulnar aspect of forearm), bone, tendons (Achilles), cartilage, and joints. Generally painless but may lead to erosions

CLINICAL FEATURES (CONT'D)

- **KIDNEYS**—urolithiasis (radiolucent), uric acid nephropathy (reversible acute renal failure secondary to acute lysis), urate nephropathy (chronic renal failure secondary to interstitial deposits)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, uric acid (sens 75%), AST, ALT, ALP, bilirubin, TSH, urinalysis, 24-h urine uric acid collection (<800 mg/day suggests ↓ excretion)
- **IMAGING**—joint XR, dual energy CT
- **ARTHROCENTESIS**—**★3C★** (**C**ell count with diff, **C**ulture and Gram stain, **C**rystal, for gout, sens 85%, spc 100%)

SPECIAL

- **TOPHI ASPIRATION**

DIAGNOSTIC ISSUES

SERUM URIC ACID LEVELS—may be falsely lowered in an acute attack

JOINT X-RAY—soft tissue swelling, normal joint space, erosions ("punched out" and sclerotic lesions with overhanging edge)

JOINT FLUID—ALWAYS confirm diagnosis with a synovial fluid tap if possible. Microscopy shows predominantly neutrophilic infiltrate with some intracellular monosodium urate crystals (needle shaped, negative birefringence, i.e. yellow when parallel to plane of polarized light)

MANAGEMENT

ACUTE—**NSAIDs** (first line, avoid if renal/hepatic failure; *naproxen* 375–500 mg PO BID × 3 days, then 250–375 mg PO BID × 4–7 days; *sulindac* 150–200 mg PO BID × 7–10 days;

MANAGEMENT (CONT'D)

indomethacin 25–50 mg PO TID × 3 days, then 100 mg PO div BID–QID × 4–7 days; *celecoxib* 200 mg PO BID × 1 day, then 100 mg PO BID × 6–10 days). **Systemic corticosteroids** (avoid if joint sepsis not excluded; *prednisone* 30–60 mg PO daily × 3 days, then ↓ 10–15 mg daily × 3 days until discontinuation, *triamcinolone* 50 mg IM × 1 dose). **Intra-articular corticosteroids** (for mono- and oligoarthritis only. *Methylprednisolone* 40–80 mg intra-articularly once). ***Colchicine*** 0.6 mg PO daily-BID during acute attack (avoid the approach of giving colchicine q1h until development of diarrhea). Low dose colchicine regimens (≤1.8 g daily) appear as effective and are better tolerated than higher dose regimens

LONG-TERM MANAGEMENT—purine-restricted diet (↓ red meats, ↓ seafood, ↑ low-fat dairy products, ↑ fruit and veggies) have limited supportive evidence. Avoidance of beer and sugar-laden beverages is beneficial. ***Allopurinol*** 50–300 mg PO daily (first line, xanthine oxidase inhibitor, renal dose adjustment required, urate-lowering therapy generally not started in acute attack; however, continue allopurinol if already on it prior to acute attack). ***Febuxostat*** 80 mg PO daily is a newer xanthine oxidase inhibitor that can be used in patients intolerant of allopurinol or in those with mild-to-moderate renal failure. ***Probenecid*** 250–1000 mg PO BID (first line, ↓ renal urate reabsorption. Ensure normal renal function). ***Sulfinpyrazone*** 50–200 mg PO BID. ***Colchicine*** 0.6 mg PO BID × 6 months (for prophylaxis against recurrent attacks only. Do not give colchicine IV)

TREATMENT ISSUES

LONG-TERM THERAPY—consider if patients have frequent attacks (≥3/year, tophaceous deposits, overproduction of uric acid, or continued cyclosporine treatment)

ALLOPURINOL OR FEBUXOSTAT TREATMENT—remember to start colchicine or NSAIDs prior to allopurinol and to overlap therapy to prevent precipitating flare. Allopurinol alone can cause an abrupt decrease in serum uric acid → breakdown and release of synovial urate crystal deposits → inflammation. Aim to decrease serum uric acid level below 362 μmol/L [5.1 mg/dL]. Do not start or stop allopurinol during an acute attack

SPECIFIC ENTITIES

CALCIUM PYROPHOSPHATE DEPOSITION DISEASE (CPPD, pseudogout)—associated with normal urate levels and chondrocalcinosis that may be visible radiographically. Crystals appear rhomboid and have positive birefringence (blue when parallel to polarized light, yellow when perpendicular). Risk factors include old age, advanced osteoarthritis, neuropathic joint, gout, hyperparathyroidism, hemochromatosis, diabetes, hypothyroidism, hypomagnesemia, trauma, and symptoms

BASIC CALCIUM PHOSPHATE CRYSTALS (BCPC)—crystals appear snowball-like with Alizarin red S stain. Implicated in bursitis, inflammation superimposed on osteoarthritis, and calcinosis cutis in systemic sclerosis and CREST

DIALYSIS PATIENTS—develop destructive arthritis and tendonitis from calcium oxalate, monosodium urate, calcium pyrophosphate, and basic calcium phosphate crystals. Amyloidosis may also contribute to arthritis

Polyarticular Joint Pain and Fever — NEJM 1994 330:11

DIFFERENTIAL DIAGNOSIS

★RICE★

RHEUMATOLOGIC

- **SEROPOSITIVE**—SLE, rheumatoid arthritis
- **SERONEGATIVE**—psoriatic arthritis, enteric arthritis, reactive arthritis, ankylosing spondylitis

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **VASCULITIS**—polymyalgia rheumatica, granulomatosis with polyangiitis, Behcet's disease, Still's disease

INFECTIONS

- **BACTERIAL**—septic (Gonococci), meningococci, endocarditis, Lyme disease, Whipple's disease, mycobacteria

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **VIRAL**—Parvovirus, rubella, HBV, HCV, HIV, EBV
- **FUNGAL**
- **POST-INFECTIOUS/REACTIVE**—enteric infections (Salmonella, Shigella, Campylobacter, Yersinia), genitourinary infections (Chlamydia), rheumatic fever, inflammatory bowel disease

CRYSTAL-INDUCED—gout, pseudogout

ETC

- **MALIGNANCIES**—acute leukemia
- **SARCOIDOSIS**—Lofgren's syndrome
- **FAMILIAL MEDITERRANEAN FEVER**
- **POLYMYALGIA RHEUMATICA**
- **MUCOCUTANEOUS DISORDERS**—dermatomyositis, erythema nodosum, erythema multiforme, pyoderma gangrenosum, pustular psoriasis

CLINICAL FEATURES

DISTINGUISHING FEATURES

- **TEMPERATURE >40 °C** [>**104 °F**]—Still's disease, bacterial arthritis, SLE
- **FEVER PRECEDING ARTHRITIS**—viral arthritis, Lyme disease, reactive arthritis, Still's disease, bacterial endocarditis
- **MORNING STIFFNESS**—RA, polymyalgia rheumatica, Still's disease, some viral/reactive arthritis
- **MIGRATORY ARTHRITIS**—rheumatic fever, gonococcemia, meningococcemia, viral arthritis, SLE, acute leukemia, Whipple's disease
- **EPISODIC RECURRENCE**—palindromic rheumatism, Lyme disease, crystal-induced arthritis, IBD, Whipple's disease, Familial Mediterranean fever, Still's disease, SLE
- **PAIN DISPROPORTIONATELY GREATER THAN EFFUSION**—rheumatic fever, Familial Mediterranean fever, acute leukemia, AIDS
- **EFFUSION DISPROPORTIONATELY GREATER THAN PAIN**—tuberculosis arthritis, bacterial endocarditis, IBD, giant cell arteritis, Lyme disease
- **SYMMETRIC SMALL JOINT SYNOVITIS**—RA, SLE, viral arthritis
- **LEUKOCYTOSIS** ($>15 \times 10^9$/L)—bacterial arthritis, bacterial endocarditis, Still's disease, systemic vasculitis, acute leukemia

CLINICAL FEATURES (CONT'D)

- **LEUKOPENIA**—SLE, viral arthritis
- **POSITIVE RHEUMATOID FACTOR**—RA (sens 70%, spc 70%), viral arthritis, tuberculosis arthritis, bacterial endocarditis, SLE, sarcoidosis, systemic vasculitis
- **POSITIVE ANTI-CYCLIC CITRULLINATED PEPTIDE ANTIBODIES** (**ACPA**)—RA (not sensitive but highly spc 95%)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, uric acid, TSH, ESR, CRP, RF, anti-CCP, ANA, serologies (*Borrelia burgdorferi*, Streptococci, Parvovirus, HBV, HCV, HIV), c-ANCA, urinalysis
- **IMAGING**—CXR, X-rays of affected joints

SPECIAL

- **ARTHROCENTESIS**—**★3C★** (**C**ell count with diff [>2000 WBC/mm^3], **C**ulture and Gram stain, **C**rystal)

MANAGEMENT

TREAT UNDERLYING CAUSE
SYMPTOM CONTROL

SPECIFIC ENTITIES

STILL'S DISEASE

- **PATHOPHYSIOLOGY**—unknown. Most consider this as a diagnosis of exclusion
- **DIAGNOSIS**—major criteria include fever ≥39 °C [≥102.2 °F] (quotidian vs. diquotidian), salmon color maculopapular rash, arthralgia/arthritis ≥2 weeks, leukocytosis. Minor criteria include pharyngitis, lymphadenopathy, abnormal liver enzymes, hepatomegaly/splenomegaly, negative ANA, and RF. Need at least 2 major criteria and 3 minor criteria to make diagnosis (sens 93%). Important to exclude infections, malignancy, and acute rheumatologic disease. Significantly elevated serum ferritin
- **TREATMENTS**—NSAIDs, corticosteroids, methotrexate, recombinant IL-1 receptor antagonist (anakinra)

Rheumatoid Arthritis

DIFFERENTIAL DIAGNOSIS OF POLYARTHRITIS

★RICE★

RHEUMATOLOGIC (>**6 weeks**)

- **SEROPOSITIVE ★PSSR★**—**P**olymyositis, **P**alindromic rheumatism, **S**LE, **S**cleroderma, **S**jogren's syndrome, **R**heumatoid arthritis
- **SERONEGATIVE ★PEAR★**—**P**soriatic arthritis, **E**nteric arthritis, **A**nkylosing spondylitis, **R**eactive arthritis, undifferentiated
- **VASCULITIS**—polymyalgia rheumatica, granulomatosis with polyangiitis, Behcet's disease, Still's disease

INFECTIONS (<**6 weeks**)

- **BACTERIAL**—sepsis, endocarditis, Lyme disease, Whipple's disease, mycobacteria
- **VIRAL**—Parvovirus, rubella, HBV, HCV, HIV
- **FUNGAL**
- **POST-INFECTIOUS/REACTIVE**—enteric infections, genitourinary infections, rheumatic fever, inflammatory bowel disease

CRYSTAL—gout, pseudogout, hydroxyapatite, basic calcium phosphate

ETC

- **MALIGNANCIES**—leukemia
- **SARCOIDOSIS**—Lofgren's syndrome
- **FAMILIAL MEDITERRANEAN FEVER**
- **MUCOCUTANEOUS DISORDERS**—dermatomyositis, erythema nodosum, erythema multiforme, pyoderma gangrenosum, pustular psoriasis, polymyalgia rheumatica

PATHOPHYSIOLOGY

CLASSIFICATION OF ARTHRITIS

- **MONOARTHRITIS**—1 joint involved
- **OLIGOARTHRITIS**—2–4 joints involved
- **POLYARTHRITIS**—≥ 5 joints involved

DESTRUCTION OF CARTILAGE—T-helper 1 mediated process → proteases produced by synovial cells destroy proteoglycans in the articular cartilage → irreversible damage 6 months to 1 year from disease onset

POSSIBLE TRIGGERS—viruses (*Parvovirus*, EBV, HTLV), super-antigens (from bacteria/viruses), autoantigens (QKRAA)

RISK FACTORS—age >50, female (3:1), first-degree relative with rheumatoid arthritis, smoking, low level of education

CLINICAL FEATURES

JOINT SYMPTOMS—symmetric polyarthritis with joint pain, swelling, redness, morning stiffness (>1 h), and dysfunction

- **HANDS**—MCP, PIP, and wrist joints most commonly involved. Deformities include Boutonniere, swan neck, Z (thumb), ulnar deviation at MCP joint, volar subluxation of proximal phalanx from MCP head, radial deviation of carpus, compression of the carpal bones, subluxation at the wrist
- **FEET**—MTP joint involved. Deformities include valgus of the ankle and hindfoot, pes planus, forefoot varus and hallux valgus, cock-up toes
- **LEGS**—knees (80%), ankles (80%), hips (50%)
- **ARMS**—shoulders (60%), elbows (50%), acromioclavicular (50%)
- **ATLANTOAXIAL**—subluxation may lead to spinal cord compression (cervical myelopathy with hand weakness/numbness)
- **TEMPOROMANDIBULAR** (30%)
- **OTHERS**—related disorders include Baker cyst, tenosynovitis, carpal tunnel syndrome

Related Topics
Gout (p. 311)
Inflammatory Myositis (p. 319)
Lupus (p. 317)
Scleroderma (p. 318)

EXTRA-ARTICULAR MANIFESTATIONS—only in seropositive patients

- **RHEUMATOID NODULES** (20%)
- **PULMONARY**—pleural effusion (exudates, low glucose), pulmonary nodules (Caplan's syndrome), acute interstitial pneumonitis, bronchiolitis obliterans
- **CARDIAC**—valvular abnormalities, myocarditis, pericardial effusion, constrictive pericarditis
- **GI**—elevated transaminases (especially ALP), nodular hyperplasia (portal hypertension, hypersplenism)
- **HEMATOLOGIC**—anemia of chronic disease, Felty syndrome (triad of seropositive rheuma-

CLINICAL FEATURES (CONT'D)

toid arthritis, neutropenia often associated with anemia and thrombocytopenia and splenomegaly. Patients at risk of life-threatening bacterial infections). Large granular lymphocyte leukemia, lymphoma

- **NEUROLOGIC**—peripheral sensory neuropathy (not motor), myelopathy from cervical vertebral subluxation
- **OPHTHALMIC**—keratoconjunctivitis sicca (Sjogren's syndrome), scleritis, episcleritis
- **DERMATOLOGIC**—vasculitis (digital arteritis, cutaneous ulceration, visceral arteritis)
- **OTHERS**—amyloidosis

CONSTITUTIONAL SYMPTOMS—fatigue (40%), fever (low grade), sweats, weight loss, myalgia

DISTINGUISHING FEATURES BETWEEN INFLAMMATORY AND NON-NFLAMMATORY ARTHRITIS

	Inflammatory	Non-inflammatory
Classic example	RA	OA
Morning stiffness	>1 h	+/–
Resting	Worsens	Improves
Activity	Improves	Worsens
Synovitis, redness	+	–
Fever, weight loss	+	–
ESR, CRP, platelets	↑	No change

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, ESR, CRP, RF (IgM), anti-CCP (more specific), ANA, urinalysis
- **IMAGING**—X-rays of affected joints (particularly hands, knees, and ankles; soft tissue swelling, periarticular osteopenia, narrowing of joint space, marginal bony erosions, subluxation, joint destruction, bony ankylosis)

SPECIAL

- **INFECTIOUS WORKUP**—serologies (Parvovirus, HBV, HCV, EBV, CMV, *Borrelia burgdorferi*)
- **ARTHROCENTESIS**—**★3C★** (**C**ell count with diff [>2000 WBC/mm^3], **C**ulture and Gram stain, **C**rystal. Cannot make definite diagnosis of rheumatoid arthritis from arthrocentesis)

DIAGNOSTIC AND PROGNOSTIC ISSUES

ACR DIAGNOSTIC CRITERIA FOR RHEUMATOID ARTHRITIS—add score of categories A to D, with a score of ≥6/10 classified as definite RA

A. **JOINT INVOLVEMENT**—one large joint (0), 2–10 large joints (1), 1–3 small joints with or without involvement of large joints (2), 4–10 small joints with or without involvement of large joints (3), >10 joints with at least 1 small joint (5);
B. **SEROLOGY**—negative RF and negative anti-citrullinated protein antibodies (ACPA) (0), low-positive RF or low-positive ACPA (2), high-positive RF or high-positive ACPA (3);
C. **ACUTE PHASE REACTANTS**—normal CRP and normal ESR (0), abnormal CRP or abnormal ESR (1);
D. **DURATION OF SYMPTOMS**— < 6 weeks (0), ≥6 weeks (1)

PROGNOSIS—increased number of joints involved, presence of rheumatoid nodules, erosions, elevated inflammatory markers and seropositivity all suggest more severe disease

MANAGEMENT

SYMPTOM CONTROL—**physical therapy**, **diet** (Ω-3 fatty acids). **Joint protection** (range of motion exercises, orthotics, splints). **NSAIDs** (anti-inflammatory dose). **Intraarticular steroid injections** (if severe pain). **Patient education**

DISEASE-MODIFYING AGENTS OF RHEUMATOID DISEASE (DMARDs)—**single agent** (methotrexate with folic acid, sulfasalazine, hydroxychloroquine, cyclosporine, gold). **Combination triple therapy** (methotrexate plus sulfasalazine plus hydroxychloroquine). **Selective pyrimidine synthesis inhibitor** (leflunomide). **TNFα inhibitors** (infliximab, etanercept, adalimumab, golimumab). **B-cell inhibitor** (rituximab, an anti-CD20 monoclonal antibody). **T-lymphocyte activation inhibitor** (abatacept), IL-6 inhibition (tocilizumab). **Surgical intervention**

SPECIFIC ENTITIES

PALINDROMIC RHEUMATISM—episodic arthritis with one or more joints being affected sequentially for hours to days, and symptom-free periods in between for days to months. May be anti-CCP positive and occasionally progresses to other rheumatic disorders (RA, SLE). Treatment with hydroxychloroquine can be useful

SPECIFIC ENTITIES (CONT'D)

SJOGREN'S SYNDROME (KERATOCONJUNCTIVITIS SICCA)

- **PATHOPHYSIOLOGY**—CD4 lymphocytic infiltration of salivary and lacrimal glands
- **CAUSES**—**primary** (sicca plus episodic, nondeforming polyarthritis), **secondary** (RA, SLE, scleroderma, polyarteritis nodosa, polymyositis, HIV)
- **CLINICAL FEATURES**—sicca (dry eyes and dry mouth, along with impaired taste, parotid gland enlargement, dental caries), dyspareunia, arthralgia, arthritis, and constitutional symptoms. May be associated with Raynaud's phenomenon, cutaneous vasculitis, cerebritis, CNS vasculitis, stroke, and peripheral neuropathy
- **INVESTIGATIONS**—quantitative Ig (polyclonal IgG), RF, ANA, ENA (SS-A, SS-B). Check for secondary causes
- **TREATMENTS**—symptomatic (artificial tears, *pilocarpine* 5 mg PO QID), hydroxychloroquine, rituximab may have a role

LOFGREN'S SYNDROME—a benign self-limited form of sarcoidosis. Tetrad of erythema nodosum, hilar lymphadenopathy, arthritis (ankles and sometimes knees), and fever

SPECIFIC ENTITIES (CONT'D)

RESPIRATORY DISEASES IN RHEUMATOID ARTHRITIS

- **AIRWAY**—cricoarytenoid arthritis with central airway obstruction, bronchiectasis, obliterative bronchiolitis, chronic small airway obstruction
- **PARENCHYMA**—pneumonia (particularly with immunosuppression), interstitial fibrosis, bronchiolitis obliterans with organizing pneumonia, rheumatoid nodules, rheumatoid pneumoconiosis, apical fibrobullous disease, drug-related pneumonitis and fibrosis (methotrexate, gold, penicillamine, NSAIDs, cyclophosphamide, azathioprine, sulfasalazine)
- **VASCULAR**—pulmonary hypertension, vasculitis
- **PLEURAL**—pleuritis, pleural effusion, pleural thickening

UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE—overlap syndrome with clinical features of two or more rheumatologic disorders (RA, SLE, Sjogren's syndrome, scleroderma, inflammatory myopathies) but does not fit the diagnostic criteria for any specific disorder

MIXED CONNECTIVE TISSUE DISEASE—a specific overlap syndrome with clinical features of SLE, scleroderma, polymyositis, and antibodies to RNP. Characteristically, Raynaud's phenomenon, myositis, and synovitis are present

Systemic Lupus Erythematosus

PATHOPHYSIOLOGY

POPULATION—typically affects women aged 15–45

AUTOIMMUNE REACTION—antibody-immune complex deposition in kidneys (glomerulonephritis), autoantibodies against cell surface antigens on hematopoietic progenitor cells (anemia, neutropenia, thrombocytopenia), antiphospholipid antibodies (thrombosis)

ACR DIAGNOSTIC CRITERIA ★4-RASHES★

- **4** rashes—malar rash, discoid rash, oral ulcers (usually painless), photosensitivity
- **R**enal—proteinuria >0.5 g/day or ≥3+, or cellular casts
- **A**rthritis ≥2 peripheral joints, non-erosive
- **S**erositis—pleuritis, pericarditis
- **H**ematologic—hemolytic anemia, leukopenia $<4.0\times10^9$/L, lymphopenia $<1.5\times10^9$/L, thrombocytopenia $<100\times10^9$/L
- **E**xcitation—seizures, psychosis

PATHOPHYSIOLOGY (CONT'D)

- **S**erology—ANA, anti-dsDNA, anti-Smith, antiphospholipid antibodies, false-positive VDRL

Need ≥4 of 11 criteria (each rash counts as one criterion and ANA as a separate criterion) to meet classification criteria. Note that many patients may not ever fulfill four criteria until several years into their disease course

CLINICAL FEATURES

JOINT SYMPTOMS—symmetric non-erosive polyarthritis with joint pain, swelling, redness, morning stiffness (>1 h), and dysfunction. Sens 88%

- **HANDS**—Jaccoud's arthritis (joint deformities are unusual). Fingers and wrists may be involved
- **LEGS**—knees more commonly affected

CLINICAL FEATURES (CONT'D)

- **AVASCULAR NECROSIS**—hip, shoulder, and knee may be affected

EXTRA-ARTICULAR MANIFESTATIONS

- **PULMONARY**—pleuritis (sens 50%), pulmonary hypertension, PE, shrinking lung syndrome (dyspnea, pleuritic chest pain, progressive reduction in lung volume, elevated diaphragms)
- **CARDIAC**—pericarditis (sens 30%), myocarditis, Libman–Sacks endocarditis
- **RENAL**—proteinuria or active sediment (sens 50%), glomerulonephritis
  - **WHO CLASSIFICATION OF LUPUS NEPHRITIS**
    - **NORMAL/MINIMAL MESANGIAL LUPUS NEPHRITIS** (class I)—asymptomatic
    - **MESANGIAL PROLIFERATIVE** (class II)—mild hematuria or proteinuria
    - **FOCAL PROLIFERATIVE** (class III)—nephritic syndrome, proteinuria
    - **DIFFUSE PROLIFERATIVE** (class IV)—nephritic syndrome, nephrotic syndrome
    - **MEMBRANOUS GLOMERULONEPHRITIS** (class V)— nephrotic syndrome
    - **ADVANCED GLOMERULOSCLEROSIS** (class VI)—uremia
    - **SEVERITY**—VI > IV > III > V > II > I, consider aggressive treatment for class III, IV
- **GI**—mesenteric thrombosis and vasculitis, transaminitis/hepatitis. Corticosteroids could increase risk of peptic ulcer disease
- **HEMATOLOGIC**—anemia of chronic disease, autoimmune hemolytic anemia, lymphopenia, thrombocytopenia
- **NEUROLOGIC**—aseptic meningitis, transverse myelitis, stroke, seizures, organic brain syndrome, psychosis, depression, peripheral neuropathy
- **DERMATOLOGIC**—photosensitivity (sens 50%), malar rash (nasolabial folds spared, sens 50%), discoid lupus (erythematous papules/plaques with central hypopigmentation, atrophic scarring involving scalp and exposed skin, sens 25%), mucosal ulcers (oral, vaginal, nasal septal), alopecia, livedo reticularis, palpable purpura, Raynaud's

SEROLOGIC—ANA (sens >99%), anti-dsDNA (very specific), anti-Smith (very specific), SSA/Ro, SSB/La, RNP, antiphospholipid antibody (sens 40%)

CLINICAL FEATURES (CONT'D)

CONSTITUTIONAL SYMPTOMS—fatigue, fever (high grade), lymphadenopathy, weight loss, myalgia

LUPUS EXACERBATIONS—typically with fatigue, arthritis, mucocutaneous, renal, neurologic, and/or dermatologic involvement. Individual patients usually have a fixed pattern of presentation. Precipitants include UV exposure, medication non-adherence, infections, and pregnancy. Always consider other causes such as infections, medication side effects (steroids), and embolisms

INVESTIGATIONS

BASIC

- **BLOOD TESTS**—CBCD, lytes, urea, Cr, ESR, CRP, ANA (sensitive), anti-dsDNA (specific for SLE), C3, C4
- **URINE TESTS**—urinalysis, urine protein to Cr ratio

SPECIAL

- **INFLAMMATORY WORKUP**—ENA (anti-Smith, spc), anti-Ro/La (especially in pregnancy, associated with neonatal lupus and congenital complete heart block), antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant), cryoglobulin
- **INFECTIOUS WORKUP**—serologies (Parvovirus, HBV, HCV, EBV, CMV)
- **ARTHROCENTESIS**—**★3C★** (**C**ell count with diff [>2000 WBC/mm^3], **C**ulture and Gram stain, **C**rystal. Cannot make definite diagnosis of systemic lupus erythematosus from arthrocentesis)

MANAGEMENT

SYMPTOM CONTROL—**cutaneous lupus** (sunscreen, hydroxychloroquine). **Arthritis** (NSAIDs, hydroxychloroquine, steroids, methotrexate). **Nephritis and neuritis** (steroids, cyclophosphamide, mycophenolate mofetil). **Serositis** (NSAIDs, steroids). **Thrombocytopenia** (steroids, IVIG, rituximab, splenectomy). **Avoid exogenous estrogen**

SPECIFIC ENTITIES

DRUG-INDUCED SYSTEMIC LUPUS

- **PATHOPHYSIOLOGY**—some drugs may trigger production of autoantibodies (e.g. ANA) which may cause or precipitate drug-induced lupus in susceptible individuals

SPECIFIC ENTITIES (CONT'D)

- **CAUSES**—procainamide, hydralazine, quinidine, atenolol, anti-TNFα (infliximab, etanercept, adalimumab, golimumab), captopril, carbamazepine, chlorpromazine, enalapril, ethosuximide, hydrochlorothiazide, isoniazid, lithium, methyldopa, minocycline, minoxidil, phenytoin, primidone, statins, sulfasalazine, trimethadione
- **CLINICAL FEATURES**—compared to systemic lupus, drug-induced lupus has the following features: middle age presentation, no gender difference, affects Caucasians, acute onset, less cutaneous, renal, neurologic, and hematologic involvement, but equal joint, hepatic, and constitutional symptoms. Usually anti-histone antibody positive, anti-Smith negative, anti-dsDNA negative and normal complement levels
- **TREATMENTS**—discontinue offending drug if possible

RAYNAUD'S PHENOMENON

- **PATHOPHYSIOLOGY**—exaggerated vasoconstriction to cold, emotional stress, or exercise. Triphasic changes from white to blue to red
- **CAUSES**—**primary** (isolated Raynaud's), **secondary** (trauma [Jack hammer, vibrations], rheumatologic [SLE, scleroderma, dermatomyositis, polymyositis, rheumatoid arthritis, mixed connective tissue disease], drugs [ergots, cocaine, β-blockers, bleomycin, vinblastine, interferon], tumors [lymphoma, carcinoid syndrome, pheochromocytoma], occlusive arterial disease, hyperviscosity, hypothyroidism, Parvovirus B19, PBC)
- **CLINICAL FEATURES**—usually symmetric episodes of sharply demarcated color changes of the skin and severe pain of the digits lasting 10–15 min. Secondary causes more likely if age >40, male, ulcerations, asymmetric, involvement proximal to digits and abnormal capillary nailfold
- **TREATMENTS**—avoidance (cold, stress, smoking, sympathomimetic drugs). Keep core temperature stable. Terminate attacks early (place hands in warm water). Dihydropyridine calcium channel blockers (*nifedipine* 10–60 mg PO TID, *amlodipine* 5–20 mg PO daily), Topical nitrates, ASA, phosphodiesterase inhibitors. Anticoagulate (if antiphospholipid antibodies or surgical interventions required)

RELATED TOPIC
Cutaneous Lupus Erythematosus (p. 421)

SPECIFIC ENTITIES (CONT'D)

SCLERODERMA

- **PATHOPHYSIOLOGY**—extensive fibrosis and some degree of inflammation of skin, blood vessels, and internal organs (GI, lungs, renal, cardiac). There are four subtypes, including diffuse systemic sclerosis (progressive systemic sclerosis), limited systemic sclerosis (formerly known as ★**CREST**★ syndrome-**C**alcinosis, **R**aynaud's phenomenon, **E**sophageal dysmotility, **S**clerodactyly, **T**elangiectasias), localized scleroderma (morphea, linear), and scleroderma sine scleroderma
- **CLINICAL FEATURES**—Raynaud's phenomenon may precede skin changes for years. Usually involves the skin (starts from extremities extending proximally, progressing from edematous to fibrotic to atrophic stage. Common signs include dilated capillary loops, sclerodactyly, flexion contractures, hypopigmentation, hyperpigmentation, "coup de sabre deformity", purse lip, telangiectasia), and GI hypomotility (dry mouth, dysphagia, dyspepsia, reflux, N&V, abdominal pain, constipation, diarrhea, weight loss). The lungs (pleural effusion, pulmonary fibrosis, pulmonary hypertension), kidneys (renal crisis), and heart (pericarditis) may also be involved
- **DIAGNOSIS**—the scoring system below is based on the 2013 ACR criteria. A total score of ≥9 supports the diagnosis of definite scleroderma.
  - Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (9)
  - Skin thickening of the fingers (only count the higher score): puffy fingers (2) or sclerodactyly of the fingers distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints (4)
  - Fingertip lesions (only count the higher score): digital tip ulcers (2), fingertip pitting scars (3)
  - Telangiectasia (2)
  - Abnormal nailfold capillaries (2)
  - Pulmonary arterial hypertension and/or interstitial lung disease (2)
  - Raynaud's phenomenon (3)
  - SSc-related autoantibodies: anticentromere, anti-topoisomerase I (anti-Scl-70), or anti-RNA polymerase III (3)
- **TREATMENTS**—skin changes (consider methotrexate). Raynaud's (calcium channel blockers). GERD (proton pump inhibitor). Renal crisis (ACE inhibitors-captopril). Interstitial pneumonitis

SPECIFIC ENTITIES (CONT'D)

(steroids, azathioprine, cyclophosphamide). Pulmonary hypertension (endothelin antagonists [bosentan], phosphodiesterase inhibitors [sildenafil, tadalafil])

INFLAMMATORY MYOPATHIES

- **PATHOPHYSIOLOGY**—classified as polymyositis, dermatomyositis, and inclusion body myositis (IBM)
- **ASSOCIATIONS**—dermatomyositis is associated with malignancy (GI, lung, ovarian, breast, lymphoma) in 6–45% of patients
- **CLINICAL FEATURES**—proximal, symmetric, progressive muscle weakness developing over weeks to months, may be associated with morning stiffness. Muscle pain is not common. Extramuscular manifestations include **arthralgias**, **cardiac** (conduction abnormalities, cardiomyopathy), **respiratory** (muscle weakness, aspiration, interstitial lung disease), **skin** (Gottron's papules [dorsal aspect of MCP and IP joints/elbows/knees], heliotrope rash (over upper eyelids with periorbital edema), V rash/shawl sign [erythematous rash over upper chest/back/shoulders], periungual telangiectasia, mechanic's hand [with darkened horizontal lines across lateral and palmar aspects of fingers/hands]), and **constitutional symptoms**. Reflexes are usually normal
- **DIAGNOSIS**—symmetric proximal weakness, elevation of muscle enzymes, EMG findings consistent with inflammatory myositis, muscle biopsy consistent with inflammatory myositis. Need all four criteria for definite polymyositis, and three criteria plus skin findings for definite dermatomyositis. Important to exclude other causes of myopathies. Anti-Jo1, anti-Mi2, anti-SRP
- **TREATMENTS**—prednisone, methotrexate, azathioprine, leflunomide, IVIG, rituximab

DISTINGUISHING FEATURES BETWEEN STEROID MYOPATHY AND INFLAMMATORY MYOPATHIES

	Steroid myopathy	Inflammatory myopathies
History	Steroid use or other steroid-related symptoms	Other inflammatory myopathy symptoms
Physical	Neck flexor normal	Neck flexor weaker
Tests	CK less often ↑	CK often ↑, anti-Jo1/anti-Mi2 Ab
EMG	Normal	Abnormal activity
Stop steroid	Improves	Worsens

Seronegative Spondyloarthropathies

DIFFERENTIAL DIAGNOSIS OF OLIGOARTHRITIS

★RICE★

Rheumatologic (>**6 weeks**)

- **SEROPOSITIVE ★PSSR★**—**P**olymyositis, **P**alindromic rheumatism, **S**LE, **S**cleroderma, **R**heumatoid arthritis
- **SERONEGATIVE ★PEAR★**—**P**soriatic arthritis, **E**nteric arthritis, **A**nkylosing spondylitis, **R**eactive arthritis, undifferentiated
- **VASCULITIS**—polymyalgia rheumatica, granulomatosis with polyangiitis, Behcet's disease, Still's disease

Infections (<**6 weeks**)

- **BACTERIAL**—sepsis, endocarditis, Lyme disease, Whipple's disease, mycobacteria
- **VIRAL**—Parvovirus, rubella, HBV, HCV, HIV

DIFFERENTIAL DIAGNOSIS OF OLIGOARTHRITIS (CONT'D)

- **FUNGAL**
- **POST-INFECTIOUS/REACTIVE**—enteric infections, urogenital infections, rheumatic fever, inflammatory bowel disease

Crystal—gout, pseudogout, hydroxyapatite, basic calcium phosphate

Etc

- **MALIGNANCIES**—leukemia
- **SARCOIDOSIS**—Lofgren's syndrome
- **FAMILIAL MEDITERRANEAN FEVER**
- **MUCOCUTANEOUS DISORDERS**—dermatomyositis, erythema nodosum, erythema multiforme, pyoderma gangrenosum, pustular psoriasis polymyalgia rheumatica

CLINICAL FEATURES

CARDINAL FEATURES

- **DISTRIBUTION**—male preponderance, age 20–40
- **SPONDYLOARTHROPATHY**—spondylitis, sacroiliitis, morning stiffness >30 min
- **OLIGOARTHRITIS**—asymmetric, usually involving hands and below waist
- **ENTHESOPATHY**—inflammation at the sites of insertion of ligaments, tendons, joint capsule, and fascia to bone, with both destruction and new bone formation. This results in Achilles tendonitis, plantar fasciitis, tenosynovitis, and dactylitis/sausage fingers
- **SEROLOGY**—HLA-B27 positive, rheumatoid factor negative

BACK EXAMINATION

- **INSPECTION**—swelling, erythema, atrophy, scars, and loss of thoracic kyphosis and cervical/lumbar lordosis
- **RANGE OF MOTION**—check gait and flexion, extension, lateral bending, rotation
- **PALPATION**—tenderness over spinous processes and sacroiliac joints
- **SPECIAL TESTS**—Modified Schober's test (place mark 5 cm below and mark 10 cm above the spine at level of PSIS/L5 with patient standing. A distance increase of <5 cm [<2 in.] between the marks with the patient bending forward suggests limited lumbar flexion), finger-to-floor distance, occiput to-wall distance. Perform FABER test (SI joint stability) and straight leg raising test (sciatica)
- **EXTRAARTICULAR CHANGES**—nail pitting, onycholysis, psoriasis, tenosynovitis, dactylitis, synovitis, acute uveitis, aortic regurgitation, apical pulmonary fibrosis, chin to chest distance, occiput-to-wall distance, decreased chest expansion, cauda equine compression, and enthesitis (costochondritis, patellar and Achilles tendonitis, plantar fasciitis). Also assess for extraintestinal manifestations of inflammatory bowel disease

DISTINGUISHING FEATURES BETWEEN VARIOUS SERONEGATIVE SPONDYLOARTHROPATHIES

- **PSORIATIC ARTHRITIS**—history of psoriasis, DIP involvement
- **ENTERIC ARTHRITIS**—history of IBD
- **ANKYLOSING SPONDYLITIS**—back involvement, ankylosis (stiffness)
- **REACTIVE ARTHRITIS**—history of urethritis/cervicitis/diarrhea, eye involvement
- **UNDIFFERENTIATED**—does not fit any of the above

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, ESR, CRP, urinalysis, RF
- **IMAGING**—X-rays of affected joints (lumbosacral spine, peripheral)

SPECIAL

- **INFECTIOUS WORKUP**—HIV serology (if suspect reactive arthritis), chlamydial PCR (if suspect reactive arthritis), stool culture (if suspect reactive arthritis)
- **HLA-B27**—association with seronegative spondyloarthropathy, most commonly ankylosing spondylitis (only order once)
- **ARTHROCENTESIS**—★**3C**★ (**C**ell count with diff, **C**ulture and Gram stain, **C**rystal)

DIAGNOSTIC ISSUES

EUROPEAN SPONDYLOARTHROPATHY STUDY GROUP CRITERIA—one of inflammatory spinal pain or synovitis (asymmetric or predominantly in the lower limbs) plus one of positive family history, psoriasis, inflammatory bowel disease, urethritis/cervicitis/acute diarrhea (within 1 month prior to arthritis), alternating buttock pain, enthesopathy, sacroiliitis (sens 75%, spc 87%)

MANAGEMENT

SYMPTOM CONTROL—physical therapy, NSAIDs, glucocorticoid injections

TREAT UNDERLYING CAUSE—sulfasalazine, methotrexate, pamidronate, and anti-TNF agents. Surgery

SPECIFIC ENTITIES

ANKYLOSING SPONDYLITIS (AS)

- **CLINICAL FEATURES**—spondylitis, sacroiliitis, morning stiffness, and arthritis of the hips, knees, shoulders, and occasionally peripheral joints. Loss of lumbar lordosis and thoracic kyphosis with significant decreased range of motion and chest expansion, positive Schober's test and occiput-to-wall test. Extraarticular manifestations include anterior uveitis, C1–2 subluxation, restrictive lung disease, aortic regurgitation, conduction abnormalities, and secondary amyloidosis. Imaging reveals bamboo spine (syndesmophytes), shiny corners (squaring and increased density anteriorly of vertebral bodies), and whiskering (new bone and osteitis at tendon and ligament insertions)

SPECIFIC ENTITIES (CONT'D)

- **NEW YORK DIAGNOSTIC CRITERIA**
  - **CLINICAL CRITERIA**—low back pain and morning stiffness of >3 months, limitation of motion of the lumbar spine in both the sagittal and frontal planes, and limitation of chest expansion (<2.5 cm [1 in.])
  - **RADIOLOGIC CRITERIA**—sacroiliitis with more than minimum abnormality bilaterally or unequivocal abnormality unilaterally
  - **DIAGNOSIS**—one clinical plus one radiologic criterion = definite AS; three clinical criteria or one radiologic criterion only = probable AS
  - **ASAS CLASSIFICATION CRITERIA FOR AXIAL SPONDYLOARTHRITIS** (sens 84%, spc 83%)—patients should have ≥3 months of back pain, age of onset <45 years and either
    A. Sacroiliitis on imaging **and** at least 1 AS feature (i.e. inflammatory back pain, arthritis, enthesitis (heel), uveitis, dactylitis, psoriasis, Crohn's/ulcerative colitis, good response to NSAIDS, family history of AS, HLA-B27 positive, and elevated CRP) OR
    B. HLA-B27 positive **and** at least 2 other AS features

ENTEROPATHIC ARTHRITIS

- **PATHOPHYSIOLOGY**—10–20% of IBD patients (more common in Crohn's than ulcerative colitis). May be first sign of IBD (especially if joint pain with anemia)
- **CLINICAL FEATURES**—spondylitis, sacroiliitis, morning stiffness, and large joint arthritis correlates with the activity of colitis. Other extraintestinal manifestations of IBD include fever, clubbing, uveitis, iritis, anemia, jaundice (primary sclerosing cholangitis), aphthous ulcers (Crohn's mainly), arthritis, erythema nodosum, pyoderma gangrenosum, DVT, and amyloidosis
- **TREATMENTS**
  - **TYPE I ARTHROPATHY**—acute, pauciarticular peripheral arthritis ± spondylitis and sacroiliitis, associated with flares. Usually self-limited and resolves with treatment of IBD (but not axial arthritis)
  - **TYPE II ARTHROPATHY**—polyarticular peripheral arthritis that does not parallel bowel disease. Consider sulfasalazine, methotrexate, azathioprine, and glucocorticosteroids. Avoid NSAIDs if possible (worsens bowel symptoms)

SPECIFIC ENTITIES (CONT'D)

PSORIATIC ARTHRITIS

- **PATHOPHYSIOLOGY**—patients with psoriatic arthritis usually have psoriasis, although psoriasis can be in a first degree relative instead. Arthritis may appear after (70%), before (15%), or at the same time (15%) as skin lesions
- **CLINICAL FEATURES**—spondylitis, sacroiliitis, morning stiffness, arthritis (distal DIP joints, asymmetric oligoarthritis of lower limbs, symmetric polyarthritis, arthritis mutilans), enthesitis (Achilles tendonitis, plantar fasciitis, tenosynovitis, dactylitis), nail changes (pits, onycholysis), pitting edema, and uveitis. Imaging reveals co-existence of erosive changes and new bone formation in the distal joints with lysis of the terminal phalanges, fluffy periostitis, "pencil-in-cup" appearance, and the occurrence of both joint lysis and ankylosis in the same patient. Rheumatoid factor positive in 2–10%, CCP positive in 8–16%
- **DIAGNOSIS**—requires one major and three minor criteria
  - **MAJOR**—presence of musculoskeletal inflammation (inflammatory arthritis, enthesitis, back pain)
  - **MINOR**—skin psoriasis, nail lesions, dactylitis, negative rheumatoid factor, and juxtaarticular bone formation on X-ray
- **TREATMENTS**—methotrexate, sulfasalazine, leflunomide, anti-TNF agents

REACTIVE ARTHRITIS

★CAN'T SEE, CAN'T PEE, CAN'T CLIMB A TREE★

- **PATHOPHYSIOLOGY**—preceding/ongoing infectious disorders such as urethritis (*Chlamydia*), diarrhea (*Shigella*, *Salmonella*, *Campylobacter*, *Yersinia*) or HIV, usually within 6 weeks. Overall, 75% achieve remission within 2 years (about one-third of them may experience intermittent relapses), and 25% develop chronic disease (with 5–10% developing ankylosing spondylitis)
- **CLINICAL FEATURES**—spondylitis, sacroiliitis, morning stiffness, lower limb arthritis (asymmetric oligoarthritis of lower limbs), and enthesitis (Achilles tendonitis, plantar fasciitis, chest wall changes, and sausage fingers/toes). Other important findings include genital lesions (circinate balanitis with shallow painless ulcers on the glans or urethral meatus, urethritis, prostatitis), skin lesions (keratoderma blennorrhag-

SPECIFIC ENTITIES (CONT'D)

ica with vesicles that progress to macules, papules and nodules on palms and soles), eye lesions (conjunctivitis, iritis [acute, unilateral, photophobia, pain, redness, impaired vision]), bowel inflammation (acute enterocolitis, chronic ileocolitis), and cardiac abnormalities (aortic regurgitation, conduction abnormalities). Plain film reveals fluffy erosions, periosteal spurs, and asymmetric syndesmophytes

- **ACR DIAGNOSTIC CRITERIA**—episode of arthritis of more than 1 month with urethritis and/or cervicitis (sens 84.3%, spc 98.2%), episode of arthritis of more than 1 month and either urethritis or cervicitis, or bilateral conjunctivitis (sens 85.5%, spc 96.4%), episode of arthritis, conjunctivitis, and urethritis (sens 51%, spc 99%), episode of arthritis of more than 1 month, conjunctivitis, and urethritis (sens 48%, spc 99%)
- **TREATMENTS**—NSAIDs (pain control), sulfasalazine, anti-TNF agents, methotrexate, azathioprine, leflunomide

Related Topics
Inflammatory Bowel Disease (p. 135)
Psoriasis (p. 410)

Back Pain

NEJM 2005 353:4

DIFFERENTIAL DIAGNOSIS

MECHANICAL

- **TRAUMA**—sprain, strain, fracture
- **FRACTURE**—compression, traumatic
- **SPONDYLOSIS**—disc, annulus, facet
- **SPONDYLOLISTHESIS**

INFLAMMATORY

- **RHEUMATOLOGIC**—psoriatic arthritis, enteric arthritis, ankylosing spondylitis, reactive arthritis
- **MALIGNANCY**—multiple myeloma, epidural metastasis, leptomeningeal metastasis
- **INFECTIONS**—epidural abscess

REFERRED PAIN

- **GI**—pancreatitis, cholecystitis
- **RENAL**—stones, pyelonephritis, abscess
- **PELVIC**
- **AORTIC ANEURYSM RUPTURE**

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES: WHAT CAN THE HISTORY AND PHYSICAL EXAMINATION TELL US ABOUT LOW BACK PAIN?

HISTORY—"**history** of cancer, unexplained weight loss, pain duration >1 month, failure to improve with conservative therapy are all relatively specific for cancer pain. **IDU** or **urinary infection** suggests spinal infection. Back pain in **young men** raises possibility of ankylosing spondylitis. **Failure to improve** with rest is sensitive for systemic conditions. **Sciatica** or **pseudoclaudication** suggests neurological involvement. **Bladder dysfunction** and **saddle anesthesia** suggest cauda equina syndrome"

PHYSICAL—"**vertebral tenderness** (sensitive but not specific) and **fever** suggest spinal infection. **Straight leg raising** should be assessed bilaterally in sciatica or neurogenic claudication. In addition to back examination, **tone**, **strength**, **reflexes and sensory examination** of lower limbs should be done"

UPDATE—positive sit-to-stand test predicts upper lumbar herniation (LR+ 26, LR- 0.35). Positive crossed straight leg raise predicts disk herniation (LR+ 1.6–5.8, LR– 0.59–0.90)

JAMA 1992 268:6
The Rational Clinical Examination.
McGraw-Hill, 2009

INVESTIGATIONS

BASIC

- **IMAGING**—spine XR

SPECIAL

- **IMAGING**—CT spine, MRI spine (if surgery), myelogram (gold standard but seldom used)
- **MYELOMA WORKUP**—CBCD, lytes, urea, Cr, ESR, serum protein electrophoresis, urinary protein electrophoresis

Related Topics
Ankylosing Spondylitis (p. 320)
Radiculopathy (p. 366)
Spinal Cord Compression (p. 253)

DIAGNOSTIC FEATURES

DISTINGUISHING FEATURES BETWEEN INFLAMMATORY AND MECHANICAL BACK PAIN

	Inflammatory	Mechanical
Age	Younger	Older
Onset	Insidious	Abrupt
Duration	>3 months	Shorter
AM stiffness	++	+/–
Resting	Worsens	Improves
Activity	Improves	Worsens
Sacroiliac joints	++	–

MANAGEMENT

SYMPTOM CONTROL—pain control
TREAT UNDERLYING CAUSE—flexion and extension exercises

SPECIFIC ENTITIES

SPINAL CORD COMPRESSION—compression of spinal cord (upper motor neuron, usually above L1 level). Symptoms include lower limb weakness, increased tendon reflexes in legs, sensory loss usually 1–5 levels below cord lesion with sacral sparing (see p. 253 for more details)
CAUDA EQUINA SYNDROME—compression of lumbosacral nerve roots (lower motor neurons, mostly below L1 level). Symptoms include lower limb weakness, depressed tendon reflexes in legs, and sacral paresthesia
SCIATICA (LUMBOSACRAL RADICULOPATHY)—defined as pain radiating in the dermatomal distribution. The classic features are aching pain in the buttock and paresthesias radiating into the posterior thigh and calf or into the posterior lateral thigh and lateral foreleg. Radiating pain below the knee is more likely to indicate a true radiculopathy than radiation only to the posterior thigh
SPONDYLOLISTHESIS—forward slipping of one vertebra on another, usually as a result of repeated stress on pars interarticularis. Symptoms include sciatica and low back pain, although it can also be asymptomatic

Disc/Root	Pain	Sensory	Weakness	Reflex
C4–5 (C5)	Medial scapula, lateral upper arm	Shoulder	Deltoid, supraspinatus, infraspinatus	Supinator
C5–6 (C6)	Lateral forearm, thumb, and index finger	Thumb and index finger	Biceps, brachioradialis, wrist extension	Biceps
C6–7 (C7)	Medial scapula, posterior arm, dorsum of forearm, third finger	Posterior forearm, third finger	Triceps, wrist flexion, finger extension	Triceps
C7–T1 (C8)	Shoulder, ulnar side of forearm, fifth finger	Fifth finger	Intrinsic hand muscles, thumb flexion, and abduction	None
L3–4 (L4)	Anterior thigh	Lateral leg to medial malleolus	Hip flexion, dorsiflexion, and inversion	Knee
L4–5 (L5)	Posterior lower limb	Lateral leg, dorsal foot including first web space	Hip extension and abduction, dorsiflexion, plantarflexion, and ankle eversion and inversion	None
L5–S1 (S1)	Posterior lower limb, often to ankle	Posterior leg, lateral foot	Hip extension and abduction, dorsiflexion, plantarflexion, and ankle eversion	Ankle
S2–S4	Sacral or buttock, radiate to posterior leg or perineum	Perineum (sacral paresthesia)	Bowel and bladder dysfunction	None

SPECIFIC ENTITIES (CONT'D)

DISC HERNIATION—prolapse of nucleus pulposus through the annulus, due to intervertebral pressure and degeneration of the ligamentous fibers. Occurs more commonly in younger patients. If the prolapsed material presses on a nerve root, may cause inflammation and sciatic symptoms. Over 95% of herniated discs affect the L4–5 or L5–S1 interspace. Most herniated discs resolve in 1–2 weeks with conservative treatment

SPECIFIC ENTITIES (CONT'D)

SPINAL STENOSIS

- **PATHOPHYSIOLOGY**—narrowing of the spinal canal, with compression of nerve roots → exerts pressure on venules around nerve roots → ischemic nerve injury causing back pain and neurologic symptoms
- **CAUSES**—common causes include degenerative disc disease, osteoarthritis of facet joints with osteophyte and cyst formation, ligamentum flavum hypertrophy, and spondylolisthesis. Laminectomy, spinal fusion, trauma, Cushing's syndrome, Paget's disease, and acromegaly are also associated with spinal stenosis
- **CLINICAL FEATURES**—neurogenic claudication characterized by worsening back and/or lower extremity pain with walking, relieved with flexion, sitting or walking up hill. Neurologic examination may reveal motor/sensory deficits in the lower extremities. The Romberg test may show wide-based gait and unsteadiness
- **DIAGNOSIS**—CT/MRI spine, lumbar myelogram
- **TREATMENTS**—pain control (acetaminophen, NSAIDs, opioids, lumbar epidural corticosteroid injections), decompression surgery with laminectomy and partial facetectomy. Physiotherapy consultation

NEJM 2008 358:8

Osteoarthritis NEJM 2007 357:14

DIFFERENTIAL DIAGNOSIS

PRIMARY OSTEOARTHRITIS

- **GENERALIZED**—primary generalized, diffuse idiopathic skeletal hyperostosis
- **ISOLATED**—nodal, hips, erosive

SECONDARY OSTEOARTHRITIS

- **MECHANICAL**—post-traumatic, post-surgical
- **NEUROPATHIC JOINTS**—diabetes, syphilis, spinal cord injury
- **INFLAMMATORY**—RA, crystal arthropathies, infectious
- **METABOLIC**—hemochromatosis, Wilson's disease, acromegaly, Paget's disease, Cushing's syndrome, ochronosis
- **BLEEDING DYSCRASIAS**—hemophilic, warfarin use

OSTEOARTHRITIS MIMICS—inflammatory features and distribution should help to rule out inflammatory arthritis (seropositive, seronegative, crystal, infectious arthropathies). Important to try to distinguish from periarticular structures (tendonitis, bursitis)

PATHOPHYSIOLOGY

ARTICULAR CARTILAGE—not due to wear and tear but involves increased activity of cartilage matrix formation and removal. As the repair effort becomes inadequate, metalloproteinases and collagenase cause degradation of cartilage and subsequent degeneration of surrounding soft tissues

PATHOPHYSIOLOGY (CONT'D)

RISK FACTORS FOR PRIMARY OSTEOARTHRITIS—age, female, obesity, high bone mass, mechanical factors (previous joint injury, excessive varus, or valgus), smoking, genetics

CLINICAL FEATURES

SUBTYPES OF PRIMARY OSTEOARTHRITIS

- **GENERALIZED**—affects DIP (Heberden's nodes), PIP (Bouchard's nodes) and first CMC joints, hips, knees, and spine. More common in women
- **ISOLATED NODAL**—affects DIP joints only. More common in women
- **ISOLATED** —affects hips only. More common in men
- **EROSIVE**—affects DIP and PIP joints, with episodes of local inflammation, mucous cyst formation, and bony erosion resulting in joint deformity. Genetic predisposition. May mimic rheumatoid arthritis
- **DIFFUSE IDIOPATHIC SKELETAL HYPEROSTOSIS** (DISH)—affects spine mainly but peripheral joints may also be involved, with osteophytes connecting ≥4 vertebrae. Also known as Forestier disease. X-rays are diagnostic. May mimic ankylosing spondylitis

INVESTIGATIONS

IMAGING—X-ray of affected joints (joint space narrowing, marginal osteophytes, subchondral sclerosis, and cysts)

DIAGNOSTIC ISSUES

DISTINGUISHING FEATURES BETWEEN PRIMARY AND SECONDARY OSTEOARTHRITIS—primary osteoarthritis almost never involves the shoulders, elbows, ankles, MCP joints, or ulnar side of wrist. Should consider secondary osteoarthritis if unusual sites for primary osteoarthritis or widespread chondrocalcinosis

ACR DIAGNOSTIC CRITERIA FOR HAND OSTEOARTHRITIS—hand pain, aching, or stiffness and three or four of the following features (hard tissue enlargement of 2 or more of 10 selected joints [second and third DIP and PIP, first CMC], hard tissue enlargement of 2 or more DIP joints, fewer than 3 swollen MCP joints, deformity of at least 1 of 10 selected joints). Sens 94%, spc 87%

ACR DIAGNOSTIC CRITERIA FOR HIP OSTEOARTHRITIS—hip pain and at least two of the following three features: ESR <20 mm/h, radiographic femoral or acetabular osteophytes, radiographic joint space narrowing. Sens 89%, spc 91%

MANAGEMENT

CONSERVATIVE MEASURES—patient education, weight reduction, exercise, physiotherapy, assistive devices (use cane to support unaffected side)

SYMPTOM CONTROL—*acetaminophen* 325–650 mg PO q4–6 h, NSAIDs (use lowest effective dose and add proton pump inhibitor for gastric protection if indicated. *Naproxen* 200–500 mg BID, *ibuprofen* 200–800 mg QID, *diclofenac gel* 5% apply to affected area QID), capsaicin cream, intra-articular glucocorticoids, intra-articular hyaluronic acid, acupuncture, glucosamine, and chondroitin sulfate. No medical treatment shown to slow progression. Splints and braces may also be useful sometimes

MANAGEMENT (CONT'D)

JOINT REPLACEMENT—indicated if uncontrollable pain or joint instability

SPECIFIC ENTITIES

POST-TRAUMATIC SECONDARY OSTEOARTHRITIS—usually isolated large joints. Knee OA may develop after meniscal tear, and shoulder OA may develop with long-standing rotator cuff injury

HEMOCHROMATOSIS—classically affects second and third MCP and shoulders mainly (see p. 482 for more details).

AVASCULAR NECROSIS/ASEPTIC NECROSIS

- **PATHOPHYSIOLOGY**—damage to vasculature from mechanical interruption, thrombosis/embolism, vessel wall injury, or venous occlusion, leading to medullary infarction. Affects the femoral head, tibial plateau, humeral head, scaphoid, and vertebrae more commonly
- **ASSOCIATIONS**—★**ASEPTIC**★ **A**lcohol, **S**teroids, **S**epsis, **S**torage disease (Gaucher), **S**ickle cell disease, **E**mboli (fat, cholesterol), **Post-radiation**, **T**rauma, **I**diopathic, **C**onnective tissue disease (SLE, rheumatoid arthritis, vasculitis), **C**ancer, hyper**C**oagulable states
- **CLINICAL FEATURES**—joint pain. Have high index of suspicion, especially if prior use of high-dose steroids
- **DIAGNOSIS**—plain radiograph (initially appears normal), CT, bone scan. MRI is the most sensitive test
- **TREATMENTS**—stop offending agents. Avoid weight bearing. Pain control. Orthopedic consult for possible debridement, decompression, or joint replacement

Fibromyalgia

DIFFERENTIAL DIAGNOSIS OF DIFFUSE BODY PAIN

FIBROMYALGIA

MYOPATHY—metabolic (hypothyroidism), drug induced, myofascial pain syndrome (more localized)

NEUROLOGIC—multiple sclerosis

PSYCHIATRIC—depression

PATHOPHYSIOLOGY

INCREASED PAIN PERCEPTION

ASSOCIATIONS— irritable bowel syndrome, irritable bladder syndrome, chronic headaches, mood disorders (depression, anxiety), sleep disorders

CLINICAL FEATURES

ACR 2010 DIAGNOSTIC CRITERIA—the diagnosis of fibromyalgia requires fulfillment of the following three criteria:

1. Widespread pain index (WPI) ≥7 and symptom severity scale score (SS) ≥5, OR WPI 3–6 and SS ≥9;
2. Symptoms present at a similar level for at least 3 months;
3. No other explanation
   - WPI is based on the number of areas in which the patient has pain over the past week (0–19): left or right shoulder girdle, left or right hip (buttock, trochanter), left or right jaw, upper or lower back, left or right

CLINICAL FEATURES (CONT'D)

upper arm, left or right lower arm, left or right upper leg, left or right lower leg, neck, chest, abdomen

- SS scale score is based on the sum of the severity of three symptoms plus the extent of somatic symptoms in general (total score 0–12)
  - Fatigue, waking unrefreshed, cognitive symptoms: for each of the 3 symptoms, indicate the level of severity over the past week using the following scale: no problem (0); slight or mild problems, generally mild or intermittent (1); moderate, considerable problems, often present or at a moderate level or both (2); severe, pervasive, continuous, life-disturbing problems (3)
  - Consider somatic symptoms in general, indicate whether the patient has no symptoms (0), few symptoms (1), a moderate number of symptoms (2), many symptoms (3)

INVESTIGATIONS

BASIC

- **LABS** (usually normal)—CBCD, lytes, urea, Cr, Ca, Mg, PO_4, ESR, TSH, CK

MANAGEMENT

REASSURANCE AND PATIENT EDUCATION PROGRAMS

LIFESTYLE—physical therapy/activity, sleep hygiene

MEDICATIONS—amitriptyline, muscle relaxants (cyclobenzaprine), SSRI/SNRIs, pregabalin

SPECIFIC ENTITIES

CHRONIC FATIGUE SYNDROME

- **DIAGNOSTIC CRITERIA**—new-onset unexplained persistent or relapsing fatigue, exclude ongoing exertion, not alleviated by rest, substantial reduction in previous activities, and at least four of the following: self-reported impairment in short term memory or concentration, sore throat, tender cervical or axillary nodes, muscle pain, multijoint pain without redness or swelling, headaches of a new pattern or severity, unrefreshing sleep, post-exertional malaise lasting >24 h
- **TREATMENTS**—cognitive behavior therapy and graded exercise

Vasculitis

NEJM 2003 349:2

DIFFERENTIAL DIAGNOSIS

PRIMARY VASCULITIDES—Takayasu aortitis, giant cell/temporal arteritis, polyarteritis nodosa (PAN), microscopic polyangiitis (MPA), Churg–Strauss syndrome, granulomatosis with polyangiitis (GPA) (formerly known as Wegener's granulomatosis)

SECONDARY VASCULITIDES (hypersensitivity)

★VASCULITIS★

- **VARIOUS DRUGS**
- **AUTOIMMUNE**—SLE, rheumatoid arthritis, Behcet's disease, relapsing polychondritis
- **SERUM SICKNESS**—penicillin
- **CRYOGLOBULINEMIA**
- **ULCERATIVE COLITIS**
- **LOW COMPLEMENT—**hypocomplementemic urticarial vasculitis
- **INFECTIONS—**viral (HBV, HCV, HIV, CMV, EBV, PARVOVIRUS B19), rickettsial
- **TUMORS—**lymphoma, multiple myeloma
- **IGA NEPHROPATHY/HENOCH–**schonlein purpura
- **SMOKING-RELATED THROMBOANGIITIS OBLITERANS**—Buerger's disease

DIFFERENTIAL DIAGNOSIS (CONT'D)

VASCULITIS MIMICS

- **RHEUMATIC DISEASES**—SLE
- **INFECTIOUS**—bacteremia, necrotic arachnidism
- **INFILTRATIVE**—amyloidosis
- **CANCER**—lymphoma
- **CONGENITAL**—coarctation of the aorta, neurofibromatosis
- **EMBOLI**—endocarditis, mycotic aneurysm, cholesterol, atrial myxoma
- **ETC**—fibromuscular dysplasia, granulomatosis/polymorphic reticulosis, ergotism, radiation fibrosis, thrombocytopenia, malignant atrophic papulosis

PATHOPHYSIOLOGY

MECHANISM—inflammation of vessel wall → loss of vessel integrity results in bleeding, and compromise of the lumen leads to tissue ischemia and necrosis. The distribution of organ involvement depends on the distribution of antigen

PATHOPHYSIOLOGY (CONT'D)

CLASSIFICATION (L = large, M = medium, S = small vessels)

- **LARGE VESSEL VASCULITIS**—Takayasu aortitis (L), giant cell/temporal arteritis (L, M)
- **MEDIUM VESSEL** (**PLUS SMALL VESSEL**) **VASCULITIS**— Kawasaki disease (L, M, S), polyarteritis nodosa (M, S), GPA (M, S), Churg–Strauss (M, S)
- **SMALL VESSELS VASCULITIS** (leukocytoclastic, hypersensitivity vasculitis)—secondary vasculitides (S)

CLINICAL FEATURES

SYMPTOMS

- **CONSTITUTIONAL**—fever, arthralgias, fatigue, anorexia
- **ORGAN ISCHEMIA**—mesenteric ischemia, stroke, blindness, peripheral neuropathy
- **SKIN CHANGES**—palpable purpura (non-blanchable), livedo reticularis, necrotic lesions, infarcts of tips of digits

PALPABLE PURPURA

- **PATHOPHYSIOLOGY**—pathognomonic of small vessel vasculitis. Inflammation of the vessel allows extravasation of blood and fluid into the extravascular space, resulting in palpable edema. Since the blood is no longer intravascular, the lesion is purpuric (non-blanchable) rather than erythematous
- **CAUSES**—inflammatory (polyarteritis nodosa, GPA, Henoch–Schonlein purpura, SLE, cryoglobulinemia), infectious (sepsis, infective endocarditis, disseminated meningococcemia), iatrogenic (drugs)
- **CLINICAL FEATURES**—bright to dark red purpuric papules/plaques
- **DIAGNOSIS**—skin biopsy shows leukocytoclastic vasculitis

CLINICAL FEATURES (CONT'D)

WHEN TO SUSPECT VASCULITIS—multi-system or ischemic vascular disease, palpable purpura, glomerulonephritis, mononeuritis multiplex, myalgia/arthralgia/arthritis, abdominal/testicular pain, unexplained constitutional symptoms. Greater likelihood of vasculitis if combination.

INVESTIGATIONS

BASIC

- **BLOOD TESTS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, albumin, ESR, CRP, ANA, urinalysis
- **IMAGING**—CXR

SPECIAL

- **INFLAMMATORY WORKUP**—RF, C3, C4, p-ANCA, c-ANCA, cryoglobulins, CK, serum protein electrophoresis
- **INFECTIOUS WORKUP**—serologies (HIV, HBV, HCV, EBV, CMV, *Treponema pallidum*, *Borrelia burgdorferi*)
- **FURTHER IMAGING GUIDED BY SYMPTOMS**—MR head, CT chest/abd/pelvis, CT/MR/conventional angiogram
- **BIOPSY OF AFFECTED ORGAN**—most important. Guided by symptoms (e.g. temporal artery, skin, kidney, GI mucosa)

DIAGNOSTIC ISSUES

DIAGNOSIS BY ORGAN INVOLVEMENT

	Head (stroke, visual Δ)	Peripheral neuropathy	Lung (dyspnea, hemoptysis)	Kidneys (GN)	Abdomen (pain)	Skin (palpable purpura)	Others
Takayasu aortitis	+						Cardiovas.
Giant cell arteritis	+						ESR++, PMR
Polyarteritis nodosa		+			+	+	GI++
Microscopic polyangiitis			+	+	+		p-ANCA
Granulomatosis with polyangiitis (GPA)	±	+	+	+			Sinus, c-ANCA
Churg-Strauss syndrome			+	+		+	Asthma, eosinophilia
Henoch-Schonlein purpura					+	+	IgA
Behcet's disease	+					+	Oral/GU/GI ulcers
Cryoglobulinemia		+		+		+	Cryoglobulin

MANAGEMENT

PRIMARY VASCULITIDES—***prednisone*** 1 mg/kg/day PO daily. ***Cyclophosphamide*** 2 mg/kg/day IV daily or 500–1000 mg/m^2 IV monthly

SECONDARY VASCULITIDES—treat underlying cause

SPECIFIC ENTITIES

TAKAYASU AORTITIS (PULSELESS DISEASE)

- **PATHOPHYSIOLOGY**—systemic vasculitis of the large arteries, typically the aorta and its branches with vessel occlusion causing MI, TIA, strokes, visual disturbances, and claudication
- **ASSOCIATIONS**—young women of Asian or Mexican descent
- **ACR DIAGNOSTIC CRITERIA**—age at disease onset <40 years, claudication of extremities, decreased brachial artery pulse, systolic blood pressure difference >10 mmHg between arms, bruit over subclavian arteries or aorta, arteriogram abnormality (narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia, or similar causes; changes usually focal or segmental). Need three of six criteria for diagnosis (sens 91%, spc 98%)
- **TREATMENTS**—steroids, DMARDs, vascular surgery, anti-platelet and anticoagulation therapy

POLYMYALGIA RHEUMATICA

- **ASSOCIATIONS**—temporal arteritis in 15%
- **CLINICAL FEATURES**—age >50, morning stiffness > pain (in proximal musculature including hip and shoulder girdle), constitutional symptoms. May have oligoarticular joint swelling (knees, wrists, shoulders), ↑ ESR. Diagnosis of exclusion

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—*prednisone* 15–20 mg PO daily at stable dose until myalgia and stiffness resolved for 2–4 weeks, then reduce by 10% (no more than 1 mg/month) every 4 weeks until tapered off. Rapid dramatic response to prednisone. Use of prednisone greater than 15 mg decreases the diagnostic specificity. Relapse is frequent

GIANT CELL ARTERITIS/TEMPORAL ARTERITIS

- **ASSOCIATIONS**—older age, polymyalgia rheumatica in 30–50%
- **CLINICAL FEATURES**—systemic vasculitis of the large and medium arteries. Temporal headache, amaurosis fugax, diplopia, jaw claudication, painful scalp nodules, and tender/palpably abnormal temporal artery. Extracranial GCA involves aorta in 10–15% of cases
- **ACR DIAGNOSTIC CRITERIA**—age >50, new-onset headache, abnormal temporal artery, ESR >50 mm/h, abnormal temporal artery biopsy. Need three of five criteria (sens 94%, spc 91%)
- **TREATMENTS**—if no ocular symptoms, *prednisone* 40–60 mg PO daily × 1 month, taper to 7.5–15 mg daily over 6–9 months, may continue for several years (monitor symptoms, signs, and CRP). If ocular symptoms present, start *methylprednisolone* 1 g IV daily × 3 days, then *prednisone* 80 mg PO daily and taper over time. Initiate therapy before biopsy if high index of suspicion. Consider methotrexate if steroid-sparing therapy required. *ASA* 81 mg PO daily is recommended to reduce vascular complications

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE TEMPORAL ARTERITIS?

	LR+	LR–
History		
Jaw claudication	4.3	0.72
Diplopia	3.5	0.96
Any headache	1.7	0.67
Temporal headache	1.5	0.82
Unilateral visual loss	0.85	1.2
Any visual symptom	1.1	0.97
Vertigo	0.71	1.1
Anorexia	1.2	0.87
Weight loss	1.3	0.89
Arthralgia	1.1	1
Fatigue	1.2	0.94

SPECIFIC ENTITIES (CONT'D)

	LR+	LR–
Fever	1.2	0.92
Myalgia	0.93	1.1
Polymyalgia rheumatica	0.97	0.99
Physical		
Beaded temporal artery	4.6	0.93
Prominent temporal artery	4.3	0.67
Tender temporal artery	2.6	0.82
Absent temporal artery pulse	2.7	0.71
Any temporal artery	2	0.53
Scalp tenderness	1.7	0.73
Optic atrophy or ischemic optic neuropathy	1.6	0.8
Any fundoscopic abnormality	1.1	1.0
Synovitis	0.41	1.1
Male gender	0.83	–
White race	1.1	–
Laboratory investigations		
Anemia	1.5	0.79
ESR abnormal	1.1	0.2
ESR >50 mm/h	1.1	0.35
ESR >100 mm/h	1.9	0.8

APPROACH—"when taking a history in a patient with possible temporal arteritis, jaw claudication and diplopia substantially increase the probability of positive biopsy results. No historical findings help rule out the diagnosis by their absence. Among physical examination findings, synovitis makes the diagnosis of temporal arteritis less likely, while beaded, prominent, enlarged, and tender temporal arteries each increase the likelihood of positive biopsy results. While these findings increase the chance of having temporal arteritis, they are variably sensitive from 16% (beaded temporal artery) to 65% (any temporal artery abnormality). The results of tests of ESR alter the likelihood of positive biopsy results. A normal ESR or ESR <50 mm/h each make positive biopsy results unlikely. Among patients clinically suspected of disease, those with an ESR >100 mm/h have a modestly increased likelihood of biopsy proven temporal arteritis. The prevalence of temporal arteritis in the general population is <1%, while it is 39% for those referred for temporal artery biopsy, suggesting that clinicians are fairly good at identifying high risk patients"

JAMA 2002 287:1

UPDATE—Temporal arteritis score >70 (for patients ≥50 years; based on headache, jaw claudication, scalp tenderness, ESR, ischemic optic neuropathy, and age) predicts positive temporal artery biopsy

The Rational Clinical Examination. McGraw-Hill, 2009

SPECIFIC ENTITIES (CONT'D)

POLYARTERITIS NODOSA (PAN)

- **PATHOPHYSIOLOGY**—necrotizing vasculitis of medium and small arteries with no glomerulonephritis. Associated with HIV, CMV, Parvovirus B19, HBV, HCV
- **CLINICAL FEATURES**—mononeuritis multiplex (particularly the peroneal and tibial branches of sciatic nerve), orchitis, skin (palpable purpura, livedo reticularis, subcutaneous nodules, distal gangrene), GI (mesenteric vasculitis), renal (vasculitis but NO glomerulonephritis)
- **ACR DIAGNOSTIC CRITERIA**—weight loss >4 kg since illness, livedo reticularis, testicular pain or tenderness, myalgias, weakness or leg tenderness, mononeuropathy or polyneuropathy, diastolic blood pressure >90 mmHg, elevated urea >14 mmol/L [>39 mg/dL] or Cr >132 μmol/L [>1.45 mg/dL], HBsAg or HBsAb positive, arteriographic abnormality (aneurysms or occlusions of the visceral arteries, not due to arteriosclerosis, fibromuscular dysplasia, or other non-inflammatory causes), biopsy of small or medium-sized artery containing PMN. Need 3 of 10 criteria (sens 82%, spc 87%)
- **TREATMENTS**—steroids, cyclophosphamide

SPECIFIC ENTITIES (CONT'D)

SPECIFIC ENTITIES (CONT'D)

MICROSCOPIC POLYANGIITIS (MPA)

- **PATHOPHYSIOLOGY**—necrotizing vasculitis of the small vessels. Frequent glomerulonephritis and lung involvement
- **CLINICAL FEATURES**—renal (RPGN), pulmonary (hemoptysis, hemorrhage). GI, skin, and neurologic symptoms as in PAN. p-ANCA positive
- **TREATMENTS**—steroids, cyclophosphamide

GRANULOMATOSIS WITH POLYANGIITIS (GPA)(formerly known as Wegener's Granulomatosis)

- **PATHOPHYSIOLOGY**—systemic vasculitis of the medium and small arteries, venules, and arterioles. Also necrotizing granulomas involving upper and lower respiratory tracts and kidneys. Associated with sinusitis and c-ANCA (autoantibodies against proteinase-3)
- **CLINICAL FEATURES ★ELKS★—E**ars and nose, **L**ungs, **K**idneys, **S**kin involvement
- **ACR DIAGNOSTIC CRITERIA**—nasal or oral inflammation/ulcers, abnormal CXR (nodules, fixed infiltrates, cavities), microhematuria (>5 RBC/HPF) or red cell casts in urine sediment, granulomatous inflammation on biopsy. Need two of four criteria for diagnosis (sens 88%, spc 92%)
- **TREATMENTS**—steroids, cyclophosphamide, methotrexate, azathioprine, rituximab

CHURG–STRAUSS SYNDROME

- **PATHOPHYSIOLOGY**—systemic vasculitis of the medium and small arteries, typically involving the lung and skin. Also vascular and extravascular granulomatosis with necrosis. Associated with asthma and p-ANCA (autoantibodies against myeloperoxidase), eosinophilia, and ↑ IgE and ESR
- **ASSOCIATIONS**—leukotriene type I receptor antagonists
- **CLINICAL FEATURES**—pneumonic infiltrate, skin rash, myocarditis, peripheral neuropathy, and nephropathy
- **ACR DIAGNOSTIC CRITERIA**—asthma, eosinophilia >10%, mono or polyneuropathy, pulmonary infiltrates (non-fixed), paranasal sinus abnormality, extravascular eosinophils. Need four of six criteria for diagnosis (sens 85%, spc 99.7%)
- **TREATMENTS**—steroids, cyclophosphamide

HENOCH–SCHONLEIN PURPURA

- **PATHOPHYSIOLOGY**—systemic vasculitis of small vessels characterized by IgA-containing immune complex deposition in tissues
- **ACR DIAGNOSTIC CRITERIA**—palpable purpura, age <20 at disease onset, intestinal angina, granulocytes in walls of arterioles or venules on biopsy. Need two of four criteria (sens 87%, spc 88%)
- **TREATMENTS**—usually resolves spontaneously. Consider steroids (*prednisone* 1 mg/kg PO daily, taper by 5–10 mg/week) for symptom control. Consider cyclophosphamide plus high-dose steroids if crescentic glomerulonephritis

BEHCET'S DISEASE

- **PATHOPHYSIOLOGY**—systemic vasculitis of the large, medium, and small arteries, typically involving the oral mucosa, eyes, skin, and CNS
- **CLINICAL FEATURES**—occurs more commonly along the Silk Route of Asia and Europe. Typically involves painful aphthous ulcers (gingival, tongue, buccal), eyes (iritis, anterior uveitis), skin (erythema nodosum, pseudofolliculitis, acneiform nodules), painful genital ulcers, joints (non-deforming monoarthritis, sometimes oligo- or polyarthritis), venous thrombosis (vena cava, portal, hepatic veins, extremities), and CNS (aseptic meningitis, meningoencephalitis, focal neurological deficits)
- **DIAGNOSTIC CRITERIA**—oral aphthous ulcers recurring ≥3× over 1 year, plus two of the following: recurrent genital aphthous ulcers, eyes features, skin features, and positive pathergy testing at 24–48 h
- **TREATMENTS**—steroids, colchicine and others (lesion dependent)

Approach to Serologies

INFLAMMATORY MARKERS

ERYTHROCYTE SEDIMENTATION RATE (ESR) (non-specific)

- **DISORDERS**—elevated in vasculitis such as temporal arteritis and polymyalgia rheumatica and almost all inflammatory disorders (rheumatologic, infectious, malignancy), anemia, renal disease, pregnancy, birth control pills, thyroid disease, and old age
- **UTILITY**—associated with disease activity in temporal arteritis and polymyalgia rheumatica. Normal value corrected for age and is usually less than [age in years + 10 (if female)]/2

C-REACTIVE PROTEIN (CRP) (non-specific)

- **DISORDERS**—elevated in vasculitis such as temporal arteritis and polymyalgia rheumatica and almost all inflammatory disorders (rheumatologic, infectious, malignancy), obesity, diabetes, CAD, and smoking
- **UTILITY**—associated with disease activity in temporal arteritis and polymyalgia rheumatica

RHEUMATOID ARTHRITIS

RHEUMATOID FACTOR—polyclonal IgM against Fc portion of IgG (non-specific)

- **DISORDERS**—significantly elevated in rheumatoid arthritis (sens 80%), Sjogren's syndrome, mixed cryoglobulinemia, and subacute bacterial endocarditis. Somewhat elevated in other rheumatologic diseases (SLE, MCTD, polymyositis, sarcoidosis), pulmonary and hepatic diseases, infections, and malignancy. May also be positive in the normal elderly
- **UTILITY**—seronegative rheumatoid arthritis does not have extraarticular findings. Does not correlate with disease activity

ANTICYCLIC CITRULLINATED PEPTIDES (anti-CCP) (very specific)

- **UTILITY**—very useful for diagnosis of rheumatoid arthritis (sens 70%, spc 95%).

LUPUS

ANTINUCLEAR ANTIBODIES (ANA) (non-specific but most sensitive test for SLE)

- **DISORDERS**—SLE (sens >99%), mixed connective tissue disease (sens >95%), Sjogren's syndrome (sens 75%), inflammatory myopathies (sens >75%), scleroderma (sens >60–90%), rheumatoid arthritis (sens 15–35%), and normal elderly
- **STAINING PATTERNS**
- **RIM**—most specific, SLE
  - **HOMOGENOUS**—SLE
  - **NUCLEOLAR**—scleroderma, CREST
  - **DIFFUSE**—non-specific
  - **SPECKLED**—most common, least specific, consider SLE, MCTD, scleroderma, Sjogren's
- **UTILITY**—negative ANA can help to exclude SLE, but ANA testing is not useful in known SLE patients

ANTI-DOUBLE-STRANDED DNA (most specific test for SLE)

- **DISORDERS**—elevated in SLE (sens 20–30%, spc >95%) and chronic active hepatitis. Usually not elevated in drug-induced lupus
- **UTILITY**—associated with lupus nephritis and disease activity in SLE (most useful for following disease)

ANTI-SMITH (very specific)

- **DISORDERS**—SLE. Usually not elevated in drug induced lupus
- **UTILITY**—SLE (sens 30%, spc >95%). Associated with lupus nephritis

ANTI-RNP

- **DISORDERS**—SLE, mixed connective tissue disease
- **UTILITY**—associated with milder SLE

ANTI-HISTONE

- **DISORDERS**—drug-induced lupus (sens >90%, very spc), SLE (sens >50%)

C3, C4

- **DISORDERS**—decreased in SLE, cryoglobulinemic vasculitis, Henoch–Schonlein purpura
- **UTILITY**—associated with lupus nephritis and disease activity in SLE and cryoglobulinemic vasculitis

SCLERODERMA

ANTI-SCL-70 (TOPOISOMERASE I) (very specific)
- **DISORDERS**—scleroderma (sens 20–30%, very spc)
- **UTILITY**—associated with disease activity

ANTICENTROMERE
- **DISORDERS**—CREST (sens 90%), idiopathic Raynaud's (sens 25%)

SJOGREN'S SYNDROME

ANTI-RO (SS-A)
- **DISORDERS**—Sjogren's syndrome (sens 75%), SLE (sens 25%)
- **UTILITY**—associated with sicca in other connective tissue disorders, extraglandular disease in Sjogren's syndrome, heart block in neonates with anti-Ro positive mothers, cutaneous lupus rash, photosensitivity, and thrombocytopenia in SLE

ANTI-LA (SS-B)
- **DISORDERS**—Sjogren's syndrome (sens 40%), SLE (sens 10%)
- **UTILITY**—associated with anti-Ro and benign course in SLE if no other autoantibody present except ANA

INFLAMMATORY MYOPATHIES

ANTI-JO-1—antibodies against t-RNA histidyl synthetase

INFLAMMATORY MYOPATHIES (CONT'D)

- **DISORDERS**—polymyositis (sens 30%)
- **UTILITY**—associated with deforming arthritis, "mechanic's hands", Raynaud's, and pulmonary fibrosis in dermatomyositis and polymyositis

ANTI-MI-2
- **DISORDERS**—dermatomyositis (sens 5%)
- **UTILITY**—associated with V-sign, shawl sign, cuticular overgrowth, good response to therapy, and good prognosis

ANTI-SRP—antibodies against anti-signal recognition protein
- **DISORDERS**—dermatomyositis and polymyositis

VASCULITIS

C-ANCA—autoantibodies against proteinase-3 (PR-3). Confirm by testing for antiproteinase-3
- **DISORDERS**—Wegener's granulomatosis (sens >80%) is the most common disorder

P-ANCA—autoantibodies against myeloperoxidase (MPO) (non-specific). May need to confirm with testing for anti-myeloperoxidase
- **DISORDERS**—Churg–Strauss (sens 65%), idiopathic crescentic glomerulonephritis (sens 65%), microscopic polyangiitis (sens 45%), polyarteritis nodosa (sens 15%), granulomatosis with polyangiitis (sens 10%)

Joint Examination

	Inspection (SEADS[a])	ROM (Active and Passive)	Palpation (SWAT[b])	Special tests
Shoulder	Winging of scapulae	Abduction (180°) Adduction (50°) Flexion (180°) Extension (60°) Internal rotation (90°) External rotation (90°)	Clavicle, AC joint, coracoid process, acromion, spine of scapula, greater and lesser tuberosity of humerus, biceps tendon	**Initial abduction against resistance** (supraspinatus) **External rotation against resistance** (infraspinatus and teres minor) **Internal rotation against resistance** (subscapularis) **Relocation and anterior release tests** (shoulder instability) **Biceps load I and II** (labrum tear) **Biceps tendonitis**
Hand and wrist	Boutonniere, Swan neck, subluxation @ MCP and wrist, ulnar deviation @ MCP, radial deviation @ carpus, rheumatoid nodules, Heberden's and Bouchard's nodes	Thumb flexion, extension, abduction, and adduction Finger flexion/extension Opposition Wrists flexion/extension	Wrist Carpal joints MCP joints PIP joints DIP joints	Also examine C-spine and upper limb (neurological testing) **Tinel's test**, **Phalen's test** (carpel tunnel syndrome) **Finkelstein's test** (de Quervain's tenosynovitis) Hand grip strength and function (write) Neurological testing of hand
Hip	Lumbar lordosis Gait[c]	Abduction (50°) Adduction (20°) Internal rotation (35°) External rotation (45°) Flexion (120°)	ASIS Iliac crest SI joint Greater trochanter Ischial tuberosity	**FABER test** (groin pain = hip joint, buttock pain = SI joint) **Thomas test** (hip flexion contracture) **Trendelenburg test** (weakness of gluteus medius on standing side) **Leg length discrepancy** (true and false)
Knee	Varus Valgus Genu recurvatum Baker cyst Gait[3]	Extension (20–30°) Flexion (135°) Extension (10°) Eversion (10°) Inversion (10°)	Patella, tibial tuberosity Head of tibia/fibula Joint line tenderness Femoral condyles Bursas (suprapatellar, subpatellar, infrapatellar, anserine) Bulge test, balloon test, patella tap	**Anterior drawer test**, **Lachman test**, **pivot shift** (anterior cruciate ligament) **Posterior drawer test** (posterior cruciate ligament) **Collateral ligaments** **McMurray test**, **medial–lateral grind test** (meniscal)
Ankle and foot	Varus Valgus Achilles tendon Nails, bunion Hallux valgus Metatarsus varus Pes planus Shoes	Dorsiflexion (20°) Plantarflexion (50°) Subtalar joint—inversion and eversion (5°) Forefoot joints Joints of toes	Achilles tendon Malleolus Anterior talofibular ligament Deltoid ligament Calcaneus Base of MTP Calcaneus Navicular	**Anterior drawer test** **Lateral/medial stability** **Subtalar complex stability** **Achilles tendon rupture**

[a]SEADS—Symmetry/swelling, Erythema, Atrophy, Deformity, and Surgeries/scars
[b]SWAT—Swelling/synovitis, Warmth, Anatomic landmarks, Tenderness
[c]Gait—heel strike, foot flat (mid-stance), heel off (lift off), toes off (swing)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE AN INSTABILITY OF THE SHOULDER OR A LABRUM LESION?

POSITION FOR TESTING—shoulder 90° abducted and 90° externally rotated, elbow 90° flexed for all tests described below, with the exception of biceps load for which the shoulder is 120° abducted and maximally externally rotated and the elbow is 90° flexed

	Sens (%)	Spc (%)	LR+	LR–
Clinical tests for shoulder instability				
Relocation test—applying pressure to shoulder anteriorly causes relief	85	87	6.5	0.18
Anterior release—releasing anterior pressure causes pain	92	89	8.3	0.09
Apprehension test—applying pressure to shoulder posteriorly causes pain	88	50	1.8	0.23
Clinical tests for labral tears				
Biceps load I and II tests—flexion of elbow against resistance causes pain	83	98	29	0.09
	90	96	26	0.11
Pain provocation of Mimori—passive movement from maximally supinated to pronated causes pain	100	90	7.2	0.03
Internal rotation resistance strength—internal rotation against resistance causes pain	88	96	25	0.12

APPROACH—"best evidence supports the value of the relocation and anterior release tests for diagnosis of shoulder instability. Symptoms related to labral tears remain unclear. Most promising for establishing labral tears are currently the biceps load I and II, pain provocation of Mimori, and the internal rotation resistance strength tests"

JAMA 2004 292:16

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE A TORN MENISCUS OR LIGAMENT OF THE KNEE?

	LR+	LR–
Clinical tests for anterior cruciate ligament tear		
Anterior drawer test	3.8	0.30
Lachman test	42	0.1
Lateral pivot shift test	–	–
Composite assessment	25	0.04
Clinical tests for posterior ligament tear		
Composite assessment	21	0.05
Clinical tests for meniscal tear		
McMurray test	1.3	0.8
Joint line tenderness	0.9	1.1
Joint effusion	5.7	0.7
Medial-lateral grind	4.8	0.4
Apley apprehension test	–	–
Composite assessment	2.7	0.4

APPROACH—"the complete examination for specific meniscal or ligamentous injuries of the knee performed much better than specific maneuvers, suggesting that synthesis of a group of examination maneuvers and historical items may be required for adequate diagnosis"

JAMA 2001 286:13

10
NEUROLOGY

Michael M.C. Yeung and Ronak K. Kapadia

Brain Tumors

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY

- **NEUROEPITHELIAL**
  - **GLIOMAS**
    - **ASTROCYTOMA** (30%)—pilocytic astrocytoma (WHO Grade I), diffuse astrocytoma (WHO Grade II), anaplastic (WHO Grade III), glioblastoma (WHO Grade IV, 20% of all brain tumors)
    - **OLIGODENDROGLIOMA** (4%)—low grade (WHO Grade II), anaplastic (WHO Grade III), mixed; 50–80% have 1p19q co-deletion which is associated with improved survival and favorable response to chemotherapy and/or radiation
    - **EPENDYMOMA** (2%) (WHO Grade II or III)
  - **CHOROID PLEXUS TUMORS** (WHO Grade II or III)
  - **NEURONAL AND MIXED NEURONAL-GLIAL TUMORS** (WHO Grade I or II)
  - **PINEAL PARENCHYMAL TUMORS**
  - **EMBRYONAL TUMORS** (1.7%)—medulloblastoma (WHO Grade IV), pineoblastoma, neuroblastoma, ependymoblastoma
- **CRANIAL/SPINAL NERVES**—schwannoma, neurofibroma, malignant peripheral nerve sheath tumor (malignant schwannoma, 8%)
- **MENINGES**
  - **BENIGN MENINGIOMA** (30%) (WHO Grade I)
  - **ATYPICAL MENINGIOMA** (WHO Grade II)
  - **ANAPLASTIC MENINGIOMA** (WHO Grade III)
  - **MALIGNANT NEOPLASMS**—hemangiopericytoma, chondrosarcoma, malignant fibrous histiocytoma, rhabdomyosarcoma, meningeal sarcomatosis
  - **PRIMARY MELANOCYTIC LESIONS**—diffuse melanosis, melanocytoma, malignant melanoma
- **LYMPHOMA** (3%)—malignant lymphomas, plasmacytoma, granulocytic sarcoma
- **GERM CELL**—germinoma, embryonal carcinoma, choriocarcinoma, teratoma
- **CYSTS AND TUMOR LIKE**—Rathke cleft cyst, epidermoid cyst, dermoid cyst, colloid cyst

PATHOPHYSIOLOGY (CONT'D)

- **SELLAR REGION**—pituitary adenoma (9–13%), pituitary carcinoma, craniopharyngioma (2–5%)
- **LOCAL EXTENSION FROM REGIONAL TUMORS**—paraganglioma, chordoma, chondrosarcoma
- **METASTATIC TUMORS**

RISK FACTORS

- **FAMILY HISTORY**
- **ENVIRONMENTAL**—radiation (meningioma, glioma), vinyl chloride (glioma)
- **DISEASES**—HIV (CNS lymphoma), familial adenomatous polyposis (medulloblastoma), Li–Fraumeni syndrome (astrocytomas), Turcot's syndrome (medulloblastoma, glioblastoma), neurofibromatosis (astrocytomas, nerve sheath tumours)

GLIOBLASTOMA DEVELOPMENT—in elderly patients, more likely *de novo* (primary GBM). In younger patients, more likely evolved from low-grade glioma (secondary GBM) with stepwise mutation

MANAGEMENT IN GLIOBLASTOMA—epigenetic silencing with methylation of MGMT (*O⁶-methylguanine–methyltransferase*) DNA-repair gene is both prognostic and predictive of better outcomes. Inactivation of MGMT prevents it from repairing the damage caused by alkylating agents, thus contributing to increased effectiveness of treatment

MASS EFFECT—tumors → vasogenic edema → direct compression of neurons causing demyelination and necrosis and specific neurological symptoms based on anatomical location. Also increases intracranial pressure causing headache, nausea and vomiting, papilledema, third nerve palsy, and herniation syndromes. Hydrocephalus may also occur with obstruction of third or fourth ventricle due to posterior fossa tumors

Related Topics
CNS lymphoma (p. 196)
Seizures (p. 350)
Headaches (p. 355)

D. Hui et al. (eds.), *Approach to Internal Medicine: A Resource Book for Clinical Practice*,
DOI 10.1007/978-3-319-11821-5_10, © Springer International Publishing Switzerland 2016

CLINICAL FEATURES

SYMPTOMS—headache (70%), seizure (50%, more with low-grade tumors), focal neurological deficits (motor, sensory, more with high-grade tumors), cognitive dysfunction, visual spatial dysfunction, aphasia, N&V, altered level of consciousness

SIGNS—cranial nerve examination, with particular attention to fundoscopy and visual fields (driving), cognitive assessment with MMSE or Montreal Cognitive Assessment (MoCA), speech, motor, sensory, gait, cerebellum, pronator drift, Romberg sign

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin
- **IMAGING**—MRI head, CT head
- **BIOPSY**—open biopsy, stereotactic biopsy

SPECIAL

- **MR SPECTROSCOPY**—*N*-acetylaspartate, choline, lactate
- **FUNCTIONAL MR**—blood flow

PROGNOSTIC ISSUES

PROGNOSIS FOR LOW-GRADE GLIOMAS—median survival 7–8 years, 5-year survival 50–94%; median time to recurrence 4.5 years, median survival from recurrence 12 months

PROGNOSIS FOR GLIOBLASTOMA—median survival 14 weeks with observation only, 20 weeks with resection, 36 weeks with radiation added, and 40–60 weeks with chemotherapy added

PROGNOSTIC FACTORS FOR ANAPLASTIC ASTROCYTOMA AND GLIOBLASTOMA—older age, poor Karnofsky performance status, degree of excision, neurologic deficits

MEDIAN SURVIVALS FOR OLIGODENDROGLIOMA

Oligodendroglioma	1p19q deletion	No1p19q deletion
Low grade	15 years	5 years
High grade	5–10 years	2 years

MANAGEMENT

SYMPTOM CONTROL—seizure control (phenytoin, levetiracetam, carbamazepine, lamotrigine, clobazam, valproate, topiramate), steroids may be used short term for cerebral edema with symptoms such as headaches, neurological deficits

MANAGEMENT (CONT'D)

TUMOR CONTROL

- **ASTROCYTOMA**
  - **LOW GRADE** (**GRADE II**)—maximal surgical debulking. Upfront radiation improves progression-free survival but not overall survival. Thus, it may be delayed in patients who are asymptomatic
  - **ANAPLASTIC** (**GRADE III**)—maximal surgical debulking, followed by radiation ± chemotherapy (PCV, temozolomide)
  - **GLIOBLASTOMA** (**GRADE IV**)—maximal surgical debulking, concurrent chemoradiation with temozolomide ×6 weeks, followed by 4-week break and then adjuvant temozolomide d1–5 q28d ×6
- **LOW-GRADE OLIGODENDROGLIOMA**
  - **WITH 1P19Q DELETION**—resection. Chemotherapy at progression to delay radiation is an option
  - **WITHOUT 1P19Q DELETION**—resection. Radiation may be delayed until progression or symptoms
- **HIGH-GRADE OLIGODENDROGLIOMA**
  - **WITH 1P19Q DELETION**—resection ± chemotherapy ± radiation
  - **WITHOUT 1P19Q DELETION**—resection, RT alone or concurrent chemoradiation with temozolomide ×6 weeks, followed by 4-week break and then adjuvant temozolomide d1–5 q28d ×6
  - **SALVAGE CHEMOTHERAPY FOR GLIOMAS**—nitrosoureas, bevacizumab, etoposide, carboplatin, procarbazine
  - **EPENDYMOMA**—resection ± radiation. Palliative chemotherapy may be provided with recurrence
  - **PRIMARY NEUROECTODERMAL TUMORS** (medulloblastoma, supratentorial, pineoblastoma)—resection plus craniospinal radiation for low risk tumors may be curative. Add adjuvant chemotherapy (cisplatin, etoposide, cyclophosphamide or lomustine and vincristine) for high-risk tumors
  - **MENINGIOMA**—observation if asymptomatic and no mass effect. Otherwise, resection or radiation if surgery not possible

DRIVING—the key factors that affect driving include seizures, visual fields, motor deficits, and cognition

TREATMENT ISSUES

SIDE EFFECTS OF BRAIN IRRADIATION

- **RADIONECROSIS**—contrast-enhancing focal lesion may be difficult to differentiate from recurrent brain tumor. Supportive measures
- **RADIATION-INDUCED LEUKOENCEPHALOPATHY**—occurs months to years later. Symptoms may include gait ataxia, urinary incontinence, and dementia
- **RADIATION MYELOPATHY**—associated with accumulative radiation dose to the spinal cord, peaking at 1 and 2 years. Symptoms may include Lhermitte's sign, paresthesias (pain and temperature) with progressive loss of cord function over 6 months. Supportive measures only

SPECIFIC ENTITIES

HERNIATION SYNDROMES

- **TRANSTENTORIAL**—symmetric downward displacement of the hemispheres, causing impaction of the diencephalon and midbrain into the tentorial notch → rostrocaudal deterioration with decorticate evolving to decerebrate posturing
- **UNCAL**—temporal lobe and uncus shift medially into the tentorial notch, causing compression of third nerve (pupillary dilation, eye deviation 'down and out') and contralateral cerebral peduncle (ipsilateral hemiparesis, false localizing sign)
- **TONSILLAR**—cerebellar tonsils downward into the foramen magnum compresses the medulla and upper spinal cord, resulting in rapid failure of vital functions

SPECIFIC ENTITIES (CONT'D)

BRAIN METASTASES

- **PATHOPHYSIOLOGY**—occurs in 20–40% of patients, most commonly from lung, breast, melanoma, renal cell, and gastrointestinal cancers. About 10× more frequent than primary brain tumors. Found in cerebral hemispheres, cerebellum, and brainstem 80%, 15% and 5% of the time
- **TREATMENT**—surgery plus radiation offers survival advantage over radiation alone, although <50% of brain metastases are resectable. Radiation reduces recurrence but does not improve survival

LEPTOMENINGEAL CARCINOMATOSIS

- **PATHOPHYSIOLOGY**—occurs in 5% of patients, most commonly from leukemias, non-Hodgkin's lymphoma, and solid tumours (lung, breast, and melanoma)
- **DIAGNOSIS**—CSF analysis for cytologic confirmation (multiple taps often necessary). MRI spine may also be helpful
- **TREATMENT**—median survival 4–6 weeks without treatment and may improve to 3–6 months with intrathecal therapy (methotrexate, cytarabine, thiotepa). Necrotizing leukoencephalopathy may develop months after in those who survived, particularly after combined methotrexate and radiation administration

Acute Stroke Syndromes

NEJM 2007 357:6
NEJM 2008 359:13
AHA/ASA Stroke Guidelines 2009

DIFFERENTIAL DIAGNOSIS

ISCHEMIC STROKE

- **THROMBOTIC/INTRINSIC VESSEL DISEASE**—atherosclerosis, vasculitis, vasospasm, dissection, compression, fibromuscular, hypercoagulable state
- **EMBOLIC/REMOTE ORIGIN**—cardiogenic, artery, septic, air, fat, paradoxical (from VTE)
- **GLOBAL ISCHEMIA**—MI, VT

HEMORRHAGIC STROKE

- **INTRACEREBRAL VESSEL RUPTURE**—hypertension, trauma, bleeding diatheses, amyloid angiopathy, illicit drug use, vascular malformation
- **SUBARACHNOID VESSEL RUPTURE**—aneurysm rupture, vascular malformation, bleeding diatheses, trauma, amyloid angiopathy, illicit drug use (cocaine)

DIFFERENTIAL DIAGNOSIS (CONT'D)

STROKE MIMICS (usually global rather than focal neurological symptoms) ★**DIMS**★

- **DRUG INTOXICATION/WITHDRAWAL**
- **INFECTIONS**
- **INSANITY**—conversion disorder
- **METABOLIC**—hypoglycemia, renal failure, hepatic failure, hypoxia/hypercarbia, endocrine disorders (thyrotoxicosis, myxedema, adrenal insufficiency)
- **MIGRAINES**
- **SYNCOPE**
- **SEIZURES**—Todd's paralysis
- **STRUCTURAL**—trauma, tumors, subdural hemorrhage

PATHOPHYSIOLOGY

FIVE QUESTIONS

1. Is the patient stable?
2. Is this a stroke?
3. Where is the stroke? Symptoms/signs, CT head
4. What kind of stroke? Ischemic (thrombotic, embolic, global ischemic), hemorrhagic (intracerebral, subarachnoid)
5. How to manage the patient? Thrombolytics?

PATHOPHYSIOLOGIC STROKE CLASSIFICATION

- **THROMBOTIC STROKE**
  1. **LARGE VESSEL STROKE**—most commonly due to atherothrombosis. Found at bifurcation of common carotid artery, siphon portion of common carotid artery, middle cerebral artery stem, intracranial vertebral arteries proximal to middle basilar artery, origin of vertebral arteries
  2. **SMALL VESSEL STROKE** (lacunar/penetrating vessels)—most commonly due to lipohyalinotic occlusion related to hypertension and occasionally atheroma at the origin of vessels. Found at penetrating branches of the anterior, middle, and posterior cerebral and basilar arteries
- **CARDIOAORTIC EMBOLIC STROKE**
  1. **CARDIAC SOURCES DEFINITE** (anticoagulant or antithrombotic therapy generally used)—LV thrombus, LA thrombus, rheumatic valve disease, artificial valve (mechanical, bioprosthetic), AF

PATHOPHYSIOLOGY (CONT'D)

2. **CARDIAC SOURCES DEFINITE** (anticoagulation hazardous)—bacterial endocarditis, atrial myxoma
3. **CARDIAC SOURCES POSSIBLE**—mitral annular calcification, left ventricular dysfunction, status post-MI, LA spontaneous echo contrast, PFO, ASD, mitral valve strands
4. **UNKNOWN SOURCE EMBOLIC STROKE**
5. **OTHERS**—dissection, moyamoya, primary thrombosis, cerebral mass

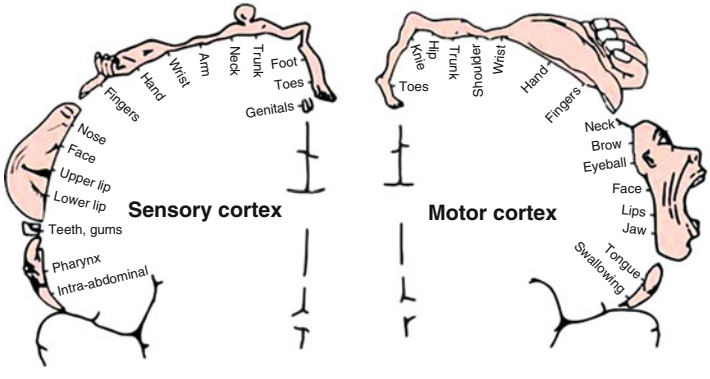
RISK FACTORS FOR STROKE

- **THROMBOTIC**—age, smoking, diabetes, dyslipidemia, hypertension, family history, male, history of TIA
- **EMBOLIC**—smoking, diabetes, dyslipidemia, hypertension, family history, male, history of heart disease (valvular, AF, endocarditis)
- **ICH**—hypertension, trauma, bleeding diatheses, illicit drugs, vascular malformations, blacks, Asians
- **SAH**—illicit drugs, bleeding diatheses

COMPLICATIONS OF STROKE—about 25% of patients can worsen during the first 24–48 h after stroke

- **NEUROLOGIC**—cerebral edema, seizures, hemorrhagic transformation of infarction with or without hematoma, neurological deficits
- **NON-NEUROLOGIC**—myocardial infarction, arrhythmia, aspiration, pneumonia, DVT, pulmonary embolism, malnutrition, pressure sores, orthopedic complications, contractures

MAP OF MOTOR/SENSORY CORTEX



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CLINICAL FEATURES

TRANSIENT ISCHEMIC ATTACK—defined as an ischemic episode with full recovery within 24 h. Most TIAs last <5 min, while most ischemic attacks >1 h are associated with infarction. Risk of stroke in patients with TIA is 5% within 2 days and 10% within 90 days

PREDICTION OF STROKE RISK AFTER TIA

- **★ABCD2★ CRITERIA**
  - **A**ge—1 = age >60 years,
  - **B**lood pressure—1 = hypertension at the acute evaluation (>140/90 mmHg)
  - **C**linical features—2 = unilateral weakness, 1 = speech disturbance without weakness
  - **D**uration of symptom—1 = 10–59 min, 2= > 60 min
  - **D**iabetes—1 = present
- **INTERPRETATION**
  - **LOW RISK** (scores 0–3) = risk of stroke 1.0% at 2 days. Hospital observation may not be necessary without another indication such as new-onset atrial fibrillation
  - **MODERATE RISK** (scores 4–5) = risk of stroke 4.1% at 2 days. Hospital observation justified in most situations
  - **HIGH RISK** (scores 6–7) = risk of stroke 8.1% at 2 days. Hospital observation recommended

CLINICAL STROKE CLASSIFICATION

- **ANTERIOR CEREBRAL ARTERY** (embolic > thrombotic)—motor and sensory deficit (leg > arm, face), frontal release signs (grasp, snout, root, and suckling reflexes), abulia, paratonic rigidity, gait apraxia, personality Δ
- **MIDDLE CEREBRAL ARTERY** (left dominant hemispheric, embolic > thrombotic)—aphasia, right hemiparesis, and sensory deficit (face, arm > leg), may be complete hemiplegia if internal capsule involved, right spatial neglect, right homonymous hemianopia, impaired right conjugate gaze
- **MIDDLE CEREBRAL ARTERY** (right non-dominant hemispheric, embolic > thrombotic)—anosognosia, left motor and sensory deficit (face, arm > leg), left spatial neglect, left homonymous hemianopia, impaired left conjugate gaze
- **DEEP (SUBCORTICAL/LACUNAR) HEMISPHERE OR BRAINSTEM** (small artery infarct)—hemiparesis (pure motor stroke); sensory loss (pure sensory stroke); dysarthria and clumsy hand syndrome; ataxic hemiparesis. No abnormalities of cognition, language, or vision
- **POSTERIOR CEREBRAL ARTERY** (embolic > thrombotic)—homonymous hemianopia with macular sparing, alexia without agraphia (dominant hemisphere), visual hallucinations, visual perseverations (calcarine cortex), choreoathetosis, spontaneous pain (thalamus), third nerve palsy, paresis of vertical eye movement, sensory loss, motor deficit (cerebral peduncle, midbrain)
- **VERTEBROBASILAR ARTERY** (brainstem, embolic = thrombotic)—motor or sensory loss in ALL 4 limbs; crossed signs (ipsilateral cranial nerve palsy with contralateral motor/sensory deficit), dysconjugate gaze, nystagmus, ataxia, dysarthria, dysphagia
- **CEREBELLUM**—ipsilateral limb ataxia, gait ataxia
- **INTERNAL CAROTID ARTERY** (thrombotic > embolic)—progressive or stuttering onset of MCA syndrome, occasionally ACA syndrome as well

RATIONAL CLINICAL EXAMINATION SERIES: IS THIS PATIENT HAVING A STROKE? PRE-TEST LIKELIHOOD—probability of a stroke among patients with neurologically relevant symptoms is 10%

	LR+	LR–
Pre-hospital assessment		
Presence of any one of acute facial paresis, arm drift, or abnormal speech	5.5	0.39
In-hospital clinical assessment	**LR+**	**Prob. stroke**
Focal neurological deficit, persistent neurological deficit, acute onset during prior week, no history of head trauma		
0 factor	0.14	1.5%
1–3 factors	–	≥10%
4 factors	40	80%

CLINICAL FEATURES (CONT'D)

NIH STROKE SCALE—**level of consciousness** (0 = alert, 1 = not alert, 2 = obtunded, 3 = unresponsive), **level of consciousness questions** (0 = answers both correctly, 1 = answers one correctly, 2 = answers neither correctly), **level of consciousness commands** (0 = performs both tasks correctly, 1 = performs one task correctly, 2 = performs neither task), **gaze** (0 = normal, 1 = partial gaze palsy, 2 = total gaze palsy), **visual fields** (0 = no visual loss, 1 = partial hemianopsia, 2 = complete hemianopsia, 3 = bilateral hemianopsia), **facial palsy** (0 = normal, 1 = minor paralysis, 2 = partial paralysis, 3 = complete paralysis), **left motor arm** (0 = no drift, 1 = drift before 5 s, 2 = falls before 10 s, 3 = no effort against gravity, 4 = no movement), **right motor arm** (0 = no drift, 1 = drift before 5 s, 2 = falls before 10 s, 3 = no effort against gravity, 4 = no movement), **left motor leg** (0 = no drift, 1 = drift before 5 s, 2 = falls before 5 s, 3 = no effort against gravity, 4 = no movement), **right motor leg** (0 = no drift, 1 = drift before 5 s, 2 = falls before 5 s, 3 = no effort against gravity, 4 = no movement), **ataxia** (0 = absent, 1 = one limb, 2 = two limbs), **sensory** (0 = normal, 1 = mild loss, 2 = severe loss), **language** (0 = normal, 1 = mild aphasia, 2 = severe aphasia, 3 = mute or global aphasia), **dysarthria** (0 = normal, 1 = mild, 2 = severe), **extinction/inattention** (0 = normal, 1 = mild, 2 = severe)

Refer to www.ninds.nih.gov/doctors/nih_stroke_scale.pdf for online version of NIH Stroke Scale

APPROACH—onset of symptoms → prehospital assessment → in-hospital assessment → if likely stroke, assess with NIH stroke score, perform neuroimaging and laboratory tests to exclude stroke mimics → begin stroke treatment. "The accurate determination of stroke subtype requires neuroimaging to distinguish ischemic from hemorrhagic stroke. Early mortality increases among those with any one of impaired consciousness, hemiplegia, and conjugate gaze palsy (LR+ 1.8, LR 0.36)"

JAMA 2005 293:19

Related Topics
CT Head (p. 378)
Dysphagia (p. 124)

CLINICAL FEATURES (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE A CLINICALLY IMPORTANT CAROTID BRUIT?

	Sens	Spc	LR+
Ability of carotid bruits to indicate carotid stenosis in symptomatic patients			
TIA patients with >50% stenosis	29%	88%	2.4
Anterior circulation TIA patients with 75–99% stenosis	76%	76%	3.2
Anterior circulation TIA patients with 70–99% stenosis	62%	61%	1.6
Ability of carotid bruit to predict carotid stenosis in asymptomatic patients			
Bruit predicting carotid stenosis (70–99%)	–	–	6.0

APPROACH—"although the presence of a carotid bruit in a patient with carotid-territory TIA/stroke increases the probability that the underlying stenosis is high grade (and therefore amenable to endarterectomy), the accuracy of this physical finding is low. Accordingly, carotid bruit cannot be used to rule in or rule out surgically amenable carotid artery stenosis in symptomatic patients. Asymptomatic preoperative bruits are not predictive of increased risk of perioperative stroke. However, they may be harbingers of transient postoperative cognitive and behavioral abnormalities"

JAMA 1993 270:23

The Rational Clinical Examination. McGraw-Hill, 2009.

CLINICAL FEATURES (CONT'D)

CLINICAL CLUES TO DIAGNOSIS

- **THROMBOTIC**—stuttering progression with periods of improvement. Lacunes develop over hours or at most a few days; large artery ischemia may evolve over longer periods. May have neck bruit or prior TIAs
- **EMBOLIC**—sudden onset with deficit maximal at onset. Clinical findings may improve quickly. Can be precipitated by getting up at night to urinate, or sudden coughing or sneezing
- **ICH**—gradual progression over minutes to hours. May be precipitated by sex or physical activities
- **SAH**—abrupt onset, thunderclap, severe headache, focal brain dysfunction less common. May be precipitated by sex or other physical activity

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE A HEMORRHAGIC STROKE?

In patients for whom clinical diagnosis of stroke has *already* been made (see JAMA 2005;293), differentiation of ischemic vs. hemorrhagic subtypes guides treatment

	LR+	LR–
Risk factors		
Coronary artery disease	0.44	1.1
Atrial fibrillation	0.44	1.1
Peripheral arterial disease	0.41	1.1
Prior TIA	0.34	1.2
Symptoms		
Seizures with neuro deficit	4.7	0.93
Vomiting	3.0	0.73
Headache	2.9	0.66
Loss of consciousness	2.6	0.65
Physical signs		
Coma	6.2	–
Neck stiffness	5.0	0.83
DBP >110 mmHg	4.3	0.59
Cervical bruit	0.12	1.1
Laboratory findings		
Xanthochromia in CSF	15	0.31
Atrial fibrillation on EKG	0.19	1.2
Clinical impression and stroke scores		
Clinician's impression hemorrhage is most likely Dx	6.2	0.28
Siriraj Stroke Score >1 (hemorrhage)	5.7	–
Siriraj Stroke Score < –1 (infarction)	0.3	–

CLINICAL FEATURES (CONT'D)

	LR+	LR–
Besson score ≥1 (hemorrhage)	1.4	–
Besson score <1 (infarction)	0.2	–

APPROACH—among stroke patients, the presence of several clinical findings such as headaches, vomiting, severe hypertension, neck stiffness, and coma increase the probability of hemorrhagic stroke. However, because these findings only have low to moderate diagnostic accuracy, neuroimaging is recommended for definitive diagnosis. Xanthochromia has high diagnostic performance but requires an invasive procedure

JAMA 2010 303:22

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, troponin, CK, PTT, INR, AST, ALT, ALP, bilirubin, total cholesterol, TGL, LDL, HDL, homocysteine, ESR
- **IMAGING**—CT head without contrast, MRI head (more sensitive than CT head in detecting acute ischemic stroke), angiogram (CT, MR, contrast), carotid dopplers, echocardiogram (TEE > TTE)

SPECIAL

- **ECG**—ST depression, QT prolongation, inverted T, prominent U waves
- **HOLTER MONITOR**—evaluation for occult atrial fibrillation
- **EEG**—if seizures
- **TOXICOLOGY SCREEN**

DIAGNOSTIC AND PROGNOSTIC ISSUES

DOMINANT HEMISPHERE—the left hemisphere is dominant (language functions) in 95% of right-handed and 70% of left-handed individuals

CT HEAD—gold standard, but relatively insensitive in detecting acute and small cortical or subcortical infarctions, especially in the posterior fossa. Critical for excluding hemorrhagic disease. Early signs (within 6 h) of MCA infarction include **hyperdense middle cerebral artery sign** (thrombus or embolus in first portion of MCA), **loss of gray-white differentiation in the cortical ribbon** (especially at the lateral margins of the insula), or lentiform nucleus and **sulcal effacement**.

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

Hypodense lesions may not appear until after 24 h. They become more hypodense overtime

MORTALITY RATE—30-day mortality post-ischemic stroke is 10–17%

PROGNOSTIC MARKERS—age, degree of neurological deficit (NIH stroke scale), extent of stroke on CT, fever

MANAGEMENT

ACUTE—**ABC**, O_2, IV, **do not treat blood pressure unless extreme** to avoid further ischemic insult (hypertensive encephalopathy or >220/120 mmHg, then *labetalol* 10 mg IV q5–10 min or 200–400 mg PO BID until BP <185/110 mmHg); for patients eligible for thrombolysis, treat if BP ≥185/110. **Thrombolytics** (if within 4.5 h of onset of ischemic stroke, see below; *alteplase* 0.9 mg/kg IV, maximum 90 mg). **Anticoagulation is not indicated** unless embolic stroke with obvious cardiac source (e.g. atrial fibrillation). ***ASA*** 81–325 mg PO daily (if thrombolytics given, may start ASA after first 24 h. For long-term secondary prophylaxis, consider clopidogrel or dipyridamole if cannot tolerate ASA). If SAH, consider nimodipine. **Neurology or neurosurgery consult**. Early mobilization/rehabilitation with multi-disciplinary team management (e.g. swallowing assessment prior to initiating diet, physiotherapy, occupational therapy). Monitor complications and treat other cardiovascular risk factors

TREATMENT ISSUES

THROMBOLYSIS

- **INCLUSION**—clinical diagnosis of ischemic stroke, age 18–80 years, onset of symptoms within 4.5 h, measurable neurological deficit, stroke symptoms present for at least 30 min with no significant improvement before treatment

TREATMENT ISSUES (CONT'D)

- **EXCLUSION**—**historical** (time of symptom onset unknown, prior history of ICH, stroke/head trauma <3 months, MI <3 months, major surgery/trauma <14 days, GI/GU bleed <21 days, arterial puncture in non-compressible site <7 days, combination of previous stroke and DM, oral anticoagulant treatment, coagulopathy), **clinical** (rapidly improving stroke symptoms, minor/isolated symptoms, seizure at onset of stroke with residual impairment secondary to postictal phenomenon, suspicion of SAH, acute MI/post-MI pericarditis, persistent hypertension ≥185/110), **labs** (platelet $<100\times10^9$/L, glucose <2.8 mM [50 mg/dL], ↑ PTT), **CT head** (hemorrhage, major early infarct signs), **severe stroke** as assessed clinically (NIH score >25) or radiographically (stroke involving >1/3 of cerebral hemisphere)
- **OUTCOME**—among patients receiving thrombolysis within 3 h of onset, favorable outcomes in 31–50% of treated patients compared to 20–38% of nontreated patients at 3 months and 1 year. Patients benefit more if treated early (<90 min) but benefit extends out to 6 h. Major risk is symptomatic brain hemorrhage (3–5%). However, mortality rate is similar between the two groups at 3 months and 1 year. Thrombolysis administered between 3 and 4.5 h after symptom onset associated with favorable outcome in 52.4% compared to 45.2% in non-treated patients, with an increased risk of intracranial hemorrhage, but no effect on mortality

RELATIVE RISK REDUCTION FOR ISCHEMIC STROKE/TIA

Condition	Primary prophylaxis	Secondary prophylaxis
Hypertension	Anti-HTN 20%	Anti-HTN 28%
Hyperlipidemia	Statins	Statins
Atrial fibrillation	ASA 20–30% Coumadin 60%	ASA 20–30% Coumadin 60%
Post-MI	ASA 31%	ASA
Post-stroke	Not needed if no previous stroke	ASA 30% Clopidogrel 43% ASA/dipyridamole 43%

The percentages in this table represent relative risk reduction

TREATMENT ISSUES (CONT'D)

CRITERIA FOR CAROTID ENDARTERECTOMY

Carotid stenosis	Symptomatic	Asymptomatic
≥70%	Yes (NNT 6.3)	Yes for men with stenosis ≥60% only (NNT 33)
50–69%	Yes for men only (NNT 22)	
<50%	No	No

Medical management (ASA) for those not eligible for carotid endarterectomy
NNT number needed to treat

SPECIFIC ENTITIES

DISTINGUISHING FEATURES BETWEEN UPPER MOTOR NEURON AND LOWER MOTOR NEURON LESIONS

	Upper motor neuron	Lower motor neuron
Inspect	Atrophy after long term	Atrophy and fasciculations
Tone	Spasticity (velocity dependent)	Flaccidity
Strength	Upper limbs flexors > extensors, pronation > supination Lower limbs extensors > flexors	Nerve root/peripheral nerve distribution
Reflex	Increased with clonus Babinski present (upgoing toe)	Decreased Babinski absent
Pronator drift	Present	Absent

SPECIFIC ENTITIES (CONT'D)

APHASIA (LANGUAGE IMPAIRMENT)

- **TESTING PHRASES**
  - **COMPREHENSION WITHOUT REPLY**—"Touch your chin, then your nose, then your ear"

SPECIFIC ENTITIES (CONT'D)

- **COMPREHENSION WITH ANSWERS**—"Do you put your shoes on before your socks?"
- **FLUENCY**—"Describe your daily activities."
- **NAMING**—"Name this object." (e.g. pen)
- **REPETITION**—"No ifs, ands, or buts."

DISTINGUISHING FEATURES BETWEEN DIFFERENT TYPES OF APHASIA

	Wernicke	Broca	Global	Anomic	Conduction	Transcortical motor	Transcortical sensory
Fluency	Normal	–	–	Normal	Normal	–	Normal
Comprehension	–	Normal	–	Normal	Normal	Normal	–
Naming	–	–	–	–	–	–	–
Repetition	–	–	–	Normal	–	Normal	Normal
Reading	–	–	–	Normal	–	+/–	–
Writing	Normal	–	–	Normal	–	+/–	–
Other associated signs		Right hemiparesis / hemisensory loss	Right hemiparesis / hemisensory loss				

SPECIFIC ENTITIES (CONT'D)

DYSARTHRIA (SPEECH IMPAIRMENT)

- **DYSARTHRIA**—speech disorder resulting from disturbances in muscular control that affects respiration, articulation, phonation, resonance, or prosody
- **DYSPHONIA**—voice disturbance in parameters of vocal quality, pitch, or intensity

Types of dysarthria	Quality
Spastic (bilateral upper motor neuron)	Harsh, strained voice Low pitch voice
Hyperkinetic (extrapyramidal [Huntington's])	Harsh, strained voice Low pitch voice Voice stoppages
Hypokinetic (extrapyramidal [Parkinson's])	Rapid rate, monopitch Low volume
Ataxic (cerebellar lesion)	Explosive, scanning speech
Flaccid (LMN [myasthenia gravis])	Breathy, nasal, low volume Wheezing

PRIMITIVE REFLEXES

- **GRASP REFLEX**—deep pressure over palmar surface results in grasp response
- **SUCK REFLEX**—insertion of an object into mouth results in sucking motion
- **ROOT REFLEX**—gentle stroking of cheek results in mouth turning toward that side
- **SNOUT REFLEX**—gentle pressure over the nasal philtrum results in puckering of lips
- **GLABELLAR TAP REFLEX**—repeated tapping forehead produces persistent blinking

Cranial Nerve Examination

CN	Nucleus location	Skull exit	Abnormalities
I	Olfactory tract	Cribriform plate	Sensory—smell (coffee, vanilla, peppermint)
II	Thalamus	Optic canal	Sensory—visual acuity and color, visual fields, blind spot, fundoscopy Reflex—pupillary reflex (afferent)
III	Midbrain	Superior orbital fissure[b]	Motor—ptosis and eye deviated downward and outward. Poor medial elevation and accommodation[d] Reflex—pupillary reflex (efferent) Parasympathetic—pupillary dilation[d]
IV	Midbrain	Superior orbital fissure[b]	Motor—patient tilts head to contralateral side, vertical diplopia worst looking to one side and down
V	Principal—Pons Spinal—pons to spinal cord Mesencephalic—midbrain Motor—Pons	V1—superior orbital fissure[b] V2—foramen rotundum V3—foramen ovale	Sensory—light touch, pain and temperature over V1, V2 and V3[e] Reflex—corneal reflex (afferent) and jaw jerk (afferent and efferent) Motor—wasting of temporal and masseter muscles, weakness of jaw movement
VI	Pons	Superior orbital fissure[b]	Motor—crossed eyes, impaired lateral gaze
VII[a]	Motor, solitary, superior salivatory—Pons to midbrain	Motor—internal acoustic meatus[c] and stylomastoid foramen Taste—stylomastoid foramen	Sensory—numbness around the ear canal and altered taste (anterior 2/3 of tongue) Motor—difficulty raising eye brows, closing eyes, frowning, blowing out cheeks and showing teeth. Altered speech ("Pa Pa Pa") and hyperacusis Reflex—Corneal reflex (efferent) Parasympathetic – lacrimation and saliva production[f]

Cranial Nerve Examination (Cont.)

CN	Nucleus location	Skull exit	Abnormalities
VIII	Vestibular, cochlear—medulla	Internal acoustic meatus[c]	Sensory—whispering, Rinne's test, Weber's test. Dix—Hallpike maneuver (if vertigo). Check for nystagmus
IX	Nucleus ambiguus, inferior salivatory, solitarius—medulla	Jugular foramen	Sensory—sensation of palate, taste (posterior 1/3 of tongue) Motor—uvula and palate movement. Speech ("Ka Ka Ka"), coughing, swallowing Reflex—gag reflex
X	Nucleus ambiguus, dorsal motor vagal, solitary—medulla	Jugular foramen	Sensory—sensation of palate Motor—uvula and palate movement. Speech ("Ka Ka Ka," hoarseness), coughing, swallowing Reflex—gag reflex
XI	Spinal accessory—cervical cord	Jugular foramen	Motor—weakness with shrugging shoulders and rotating head against resistance
XII[a]	Medulla	Hypoglossal foramen	Motor—tongue wasting and fasciculations, tongue deviation (toward affected side). Altered speech ("La La La")

[a]**UPPER MOTOR NEURON INNERVATION**—all cranial nerves receive bilateral innervation from the cortex, except for VII (lower facial muscles) and XII (tongue) which receive innervation from the contralateral pyramidal tract only. Therefore, a left MCA stroke can cause right lower facial droop and tongue deviation to the right. See Bell's palsy (p. 347) for differentiating UMN vs. LMN VII palsy

[b]**CAVERNOUS SINUS LESIONS** (tumor, aneurysm, and thrombosis)—may lead to III, IV, V1 and VI palsies

[c]**CEREBELLOPONTINE ANGLE LESIONS** (acoustic neuroma, glomus tumor)—may lead to V1–3, VII, and VIII palsies

[d]**OCULOMOTOR** (**III**) **NERVE LESIONS**—central lesions include vascular lesions and tumor of brainstem. Peripheral lesions include aneurysm, tumor, meningitis, nasopharyngeal carcinoma, orbital lesions, and ischemic lesions (diabetes, hypertension). "Pupil-sparing" suggests ischemic lesions (as opposed to compressive aneurismal lesions) as they tend to involve the central portion of the nerve, sparing the parasympathetic fibers. Spontaneous resolution of symptoms typically occurs over 3–6 months. Intact accommodation reflex but absent light reflex suggests midbrain tectal lesion (Argyll Robertson pupil in neurosyphilis)

[e]**TRIGEMINAL** (**V**) **NERVE LESIONS**—sensory function can be helpful in localization. If all three divisions (V1–V3) get affected, the lesion is likely at the ganglion or sensory root level (trigeminal neuroma, meningioma). If only a single division is affected, the lesion is likely at the post-ganglion level (e.g. V1 abnormality alone suggests cavernous sinus lesion). Loss of pain/temperature sensation but not light touch suggests brainstem or upper cord lesion (syringobulbia, PICA infarction). Loss of light touch but not pain/temperature suggests pathology of pontine nuclei (tumor, vascular lesion)

[f]**FACIAL** (**VII**) **NERVE LESIONS**—for details on localization, please refer to p. 347

SPECIFIC ENTITIES

VISUAL FIELD DEFECTS

- **MONOCULAR VISUAL LOSS**—lesion is located before optic chiasm (optic nerve, eye pathology)
- **BITEMPORAL HEMIANOPIA**—lesion is at the optic chiasm. The pituitary gland lies below the optic chiasm. A pituitary adenoma may compress the optic chiasm inferiorly, causing superior bitemporal quadranopsia and eventually complete bitemporal hemianopia
- **HOMONYMOUS HEMIANOPIA**—lesion is located post optic chiasm
- **FORMAL VISUAL FIELD TESTING**—Goldman perimeter

SPECIFIC ENTITIES (CONT'D)

OCULAR FINDINGS IN HYPERTENSION AND DIABETES

- **HYPERTENSION**—see p. 65
- **DIABETES**—see p. 381

Related Topics
Diplopia (p. 347)
Dysarthria (p. 344)
Facial Droop (p. 348)
Ptosis (p. 360)

SPECIFIC ENTITIES (CONT'D)

DISTINGUISHING FEATURES BETWEEN PAPILLEDEMA, OPTIC ATROPHY, AND OPTIC NEURITIS

	Papilledema	Optic atrophy	Optic neuritis
Etiology	↑ ICP Tumors Malignant hypertension	Neuritis Glaucoma Congenital	Multiple sclerosis
Symptoms	Headaches N&V, ↓ level of consciousness Focal deficits	↓ **vision** ↓ color	↓ **vision** ↓ color **Eye pain**
Optic disc	Swollen optic disc Disc margins obscured	Gray–white optic disc	Swollen optic disc
Other signs	Flame hemorrhages Cotton wool spots ↑ blind spot	↓ acuity ↓ color vision ↓ pupil reflex	↓ acuity ↓ color vision ↓ pupil reflex ↑ blind spot

MEDULLARY SYNDROMES

	Medial (Dejerine syndrome)	Lateral (Wallenberg syndrome)
Artery supply	Vertebral and anterior spinal arteries	Vertebral artery or posterior inferior cerebellar artery
Structures (ipsilateral)	Hypoglossal nucleus & CN XII—tongue weakness	Trigeminal nucleus & tract—↓ facial sens Vestibular nuclei—nystagmus, vertigo, nausea, ataxia Nucleus ambiguus—dysphagia, hoarseness Nucleus solitaries—altered taste Sympathetic—Horner's
Motor (contralateral)	Pyramidal tract—UMN weakness)	None
Sensory (contralateral)	Medial lemniscus—vibration, proprioception	Spinothalamic tract—↓ pain and temperature
Cerebellum (ipsilateral)	Normal	Inferior cerebellar peduncle—ataxia

Diplopia

DIFFERENTIAL DIAGNOSIS

BINOCULAR DIPLOPIA (resolves with one eye closed, suggestive of ocular misalignment)

- **CRANIAL NERVES**—III, IV, VI palsy, internuclear ophthalmoplegia
- **RECTUS MUSCLES**—myasthenia gravis, trauma

MONOCULAR DIPLOPIA (persists with one eye closed, suggestive of intrinsic eye disease)

- **CORNEA**—deformity, keratoconus
- **LENS**—cataract, displaced lens
- **RETINA**—macular scarring

PATHOPHYSIOLOGY

EXTRAOCULAR EYE MOVEMENTS

Muscle	Nerve	Movement
Superior rectus	III	Elevation and intorsion
Inferior rectus	III	Depression and extorsion
Lateral rectus	VI	Abduction
Medial rectus	III	Adduction
Superior oblique	IV	Depression and intorsion
Inferior oblique	III	Elevation and extorsion

CLINICAL FEATURES

HISTORY—determine whether diplopia resolves with one eye closed, which direction diplopia is worse, whether separation of images occur vertically, horizontally, or obliquely, whether any head position makes diplopia better, and whether diplopia is worse at distance (typically lateral rectus palsy) or near (typically medial rectus palsy). Characterize duration, progression, limitation of function and any pain. Past medical history (head injury, stroke, infections, aneurysm, myasthenia gravis) and medications

CLINICAL FEATURES (CONT'D)

PHYSICAL—inspect for eye position, corneal abrasion, cataract, ptosis (CN III palsy, myasthenia gravis), eyelid retraction (thyroid ophthalmopathy), and extraocular eye movements (each eye individually, then both eyes together). Palpate for bony tenderness. Auscultate over eye for bruit of carotid cavernous fistula. Also check visual acuity, visual fields, pupil size, pupillary reflex, exophthalmos, and examine the other cranial nerves (particularly II, V, VII)

INVESTIGATIONS

BASIC

- **IMAGING**—CT head, MR skull/orbit

SPECIAL

- **EDROPHONIUM OR ICE TEST**—if suspect myasthenia gravis

MANAGEMENT

TREAT UNDERLYING CAUSE—extraocular muscle surgery, prisms

SPECIFIC ENTITIES

INTERNUCLEAR OPHTHALMOPLEGIA (INO)

- **PATHOPHYSIOLOGY**—lesion in the medial longitudinal fasciculus (MLF), which connects the ipsilateral VI nucleus with the contralateral III nucleus
- **CAUSES**—multiple sclerosis (bilateral), brainstem infarction (unilateral), infections, malignancy, metabolic
- **CLINICAL FEATURES**—horizontal eye movement with weak adduction of the ipsilateral eye and abduction nystagmus of the contralateral eye

Bell's Palsy

NEJM 2004 351:13

CAUSES OF FACIAL DROOP

CENTRAL (upper motor neuron)—stroke

PERIPHERAL (lower motor neuron)

- **PONS**—infarction, glioma, multiple sclerosis
- **CEREBELLOPONTINE ANGLE**—acoustic or facial neuroma, meningioma, cholesteatoma, lymphoma, aneurysm, sarcoidosis
- **INTERNAL AUDITORY CANAL PROXIMAL TO OR INVOLVING GENICULATE GANGLION**—Bell's palsy, Ramsay Hunt syndrome (VZV), acoustic or facial neuroma

CAUSES OF FACIAL DROOP (CONT'D)

- **DISTAL TO INTERNAL AUDITORY CANAL AND GENICULATE GANGLION**—Bell's palsy, temporal bone fracture, cholesteatoma, glomus tumor, middle-ear infection
- **STYLOMASTOID FORAMEN**—head injury, parotid tumor

PATHOPHYSIOLOGY

INNERVATION—the upper facial muscles are innervated by both cerebral hemispheres, while the lower facial muscles are only innervated by the contralateral cerebral hemisphere. Thus, an upper motor neuron lesion would spare the upper face, while a lower motor neuron lesion would lead to ipsilateral upper and lower facial weakness

CLINICAL FEATURES

DISTINGUISHING FEATURES BETWEEN UPPER AND LOWER MOTOR NEURON FACIAL NERVE LESIONS

	Central (stroke)	Peripheral (Bell's palsy)
Lesion	Contralateral cortex or corticobulbar fibers	Ipsilateral facial nerve nucleus or facial nerve
Upper facial muscles	Furrows present Can close eyes	No furrows Cannot close eyes
Lower facial muscles	Unable to show teeth	Unable to show teeth
Salivation, taste, and lacrimation	Normal	Varies depending on lesion location[a]
Other findings	Hemiplegia (same side as palsy)	Hyperacusis

[a]Lacrimation, salivation, and taste all affected if lesion in internal auditory canal proximal to or involving geniculate ganglion. Lacrimation intact but salivation and taste both affected if lesion distal to geniculate ganglion. Lacrimation, salivation, and taste all intact if lesion in cortex, pons, cerebellopontine angle, or at stylomastoid foreman

INVESTIGATIONS

BASIC

- **LABS**—CBCD, fasting glucose

SPECIAL

- **IMAGING**—MRI head (in atypical cases)
- **CENTRAL CAUSES WORKUP**—Lyme serology, VDRL, HIV serology, lumbar puncture
- **ELECTRONEUROGRAPHY**—if persistent facial paralysis after 1 week of treatment

DIAGNOSTIC AND PROGNOSTIC ISSUES FOR BELL'S PALSY

INVESTIGATIONS—consider if other cranial nerve deficits develop, no recovery in 3–6 weeks, facial twitch or spasm precedes Bell's palsy (suggestive of tumor)

PROGNOSIS—71% of untreated patients recover spontaneously

MANAGEMENT OF BELL'S PALSY

TREAT UNDERLYING CAUSE—*prednisone* 1 mg/kg PO ×7 days (given within 3 days of onset). For severe facial weakness, consider *valacyclovir* 1 g PO TID ×7 days. Surgical decompression (only if documented 90% nerve degeneration by electroneurography)

SPECIFIC ENTITIES

RECURRENT OR BILATERAL FACIAL PALSY—Guillain–Barre syndrome, myasthenia gravis, lesions at skull base (lymphoma, sarcoidosis, Lyme disease)

RAMSAY HUNT SYNDROME—reactivation of herpes zoster virus in geniculate ganglion. Polycranial neuropathy affecting CN V, IX, X. Facial palsy, ear pain, and vesicles in external auditory meatus may be present. Taste often affected, ± vertigo. Consider antiviral therapy

Multiple Sclerosis

DIFFERENTIAL DIAGNOSIS

INFLAMMATORY DISEASES—Devic's neuromyelitis (neuromyelitis optica, combination of optic neuritis, and cervical myelopathy), acute disseminated encephalomyelitis, SLE, PAN, Sjogren's, Behcet's disease, granulomatous angiitis, paraneoplastic encephalomyelopathies
INFECTIONS—Lyme neuroborreliosis, neurosyphilis, HIV, HTLV-1, PML (JC virus)
GRANULOMATOUS DISEASES—sarcoidosis, granulomatosis with polyangiitis, lymphomatoid granulomatosis
DISEASES OF MYELIN—adult metachromatic leukodystrophy, adrenomyeloleukodystrophy
OTHERS—vitamin B12 deficiency, Arnold–Chiari malformation, spinocerebellar disorders

PATHOPHYSIOLOGY

MULTIPLE SCLEROSIS—autoimmune demyelination of the central nervous system
CLINICAL COURSE

- **RELAPSING–REMITTING**—85% at presentation, half will have more progressive disease over time. Average about 1 attack/year
- **PRIMARY PROGRESSIVE**—15% at presentation
- **SECONDARY–PROGRESSIVE**—occurring after a relapsing–remitting period
- **PROGRESSIVE–RELAPSING**—relapsing course, but with overall progression following each relapse

EXACERBATIONS—new neurological deficit or reappearance/worsening of old deficit that lasts longer than 24 h and is not due to fever or other systemic process
PSEUDO-EXACERBATIONS—transient fluctuations in neurological function due to concomitant illness (e.g. UTI), heat, or exertion that typically resolve with removal of precipitant

CLINICAL FEATURES

CRANIAL NERVES—optic neuritis (afferent pupillary defect), diplopia (internuclear ophthalmoplegia, especially if bilateral), trigeminal neuralgia, other cranial nerves
SENSORY (most common)—paresthesia, dysesthesia, hyperesthesia. Pain syndromes include trigeminal neuralgia, Lhermitte's sign (lightening bolt radiating down neck with flexion), dysesthetic pain, back pain, visceral pain, and painful tonic spasms. May be migratory (contralateral, ascending). Other sensory changes include useless hand syndrome (loss of discriminatory

CLINICAL FEATURES (CONT'D)

function and proprioception), "cold water" trickling feeling along limb, and pseudoathetosis (loss of sensory feedback from arm causing involuntary writhing movements of fingers and wrist when eyes closed)
TONE—spasms spells (maybe painful), spontaneous clonus
MOTOR—weakness, spasticity, and hyperreflexia. Upper motor neuron weakness in lower extremities characteristic of multiple sclerosis
AUTONOMIC—bladder, bowel, and erectile dysfunction
CEREBELLAR—loss of balance, action tremor, slurred speech, and incoordination
COGNITIVE—inattention, slowed information processing, memory loss, and difficulties with abstract concepts and complex reasoning
FATIGUE, DEPRESSION

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, Ca, Mg, PO_4, CK, quantitative Ig, ANA, ENA
- **IMAGING**—MRI head/spine (sens 90%)
- **LUMBAR PUNCTURE**—with CSF IgG index and oligoclonal bands (mild lymphocytosis <50/mm^3, mild ↑ protein with ≥2 oligoclonal bands)

SPECIAL

- **EVOKED POTENTIAL STUDIES**

DIAGNOSTIC AND PROGNOSTIC ISSUES

DIAGNOSTIC CRITERIA—symptoms and signs that are disseminated in time and space (i.e. more than one episode involving more than one area of the CNS based on clinical findings and/or MRI findings) using the revised McDonald criteria (2010)
PROGNOSIS—most patients initially in relapsing–remitting course experience relapses with complete or partial recovery once to twice a year. At 10 years, 50% enter secondary progressive phase and 90% by 25 years. Primary progressive disease affects 15% of patients, more commonly men. Eventually, 1/3 of patients would develop disabling paraparesis, 1/4 incontinent or catheterized, and 15% confined to wheelchair; 50% of patients unable to work at 5 years; 10% may remain minimally disabled at 10 years

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

POOR PROGNOSTIC FACTORS IN RELAPSING–REMITTING MULTIPLE SCLEROSIS—>2 exacerbations/year, motor/cerebellar exacerbations, older age at onset (greater than 40 years), residual motor/cerebellar deficits 6 months following attack, moderate disability within 5 years, number of lesions on MRI

GOOD PROGNOSTIC FACTORS IN RELAPSING–REMITTING MULTIPLE SCLEROSIS—initial presentation optic neuritis, purely sensory disorder, lower number of lesions on MRI

MANAGEMENT

EXACERBATIONS—***methylprednisolone*** 500–1000 mg IV daily×3–7 days or ***prednisone*** 1250 mg PO daily×3–7 days ± short taper. **Plasma exchange**

IMMUNOTHERAPY—no consensus guidelines. Treatment choice based on relative risks/benefits as well as patient/clinician preference. For newly-diagnosed disease, consider ***Avonex*** (*interferon β-1a* 30 µg IM weekly), ***Betaseron*** (*interferon β-1b* 250 µg SC q2days), ***Copaxone*** (*glatiramer acetate* 20 mg SC daily), ***Rebif*** (*interferon β-1a* 22–44 µg SC three times a week), ***Tecfidera*** (*dimethyl fumarate* 120 mg PO BID×7 days then 240 mg PO BID), or ***Aubagio*** (*teriflunomide* 7–14 mg PO daily). For highly active relapsing-remitting MS

MANAGEMENT (CONT'D)

with inadequate response to interferon β or glatiramer acetate, consider ***Gilenya*** (*fingolimod* 0.5 mg PO daily) or ***Tysabri*** (*natalizumab* 300 mg IV q4weeks, risk of PML)

- **RELAPSING–REMITTING**—early treatment shown to have favorable outcomes
- **PRIMARY AND SECONDARY PROGRESSIVE**—evidence does not support benefit from interferon β in primary progressive disease, and limited in secondary progressive disease

Neurology 2012 78:23
NEJM 2007 356:25
NEJM 2010 362:5
NEJM 2011 365:14
NEJM 2012 367:12

SYMPTOM CONTROL—**fatigue** (*amantadine* 100 mg PO BID; *modafinil* 100 mg PO TID), **spasticity** (physiotherapy, baclofen, tizanidine, benzodiazepines), **hyperreflexic bladder** (fluid restriction, timed voiding, oxybutynin, propantheline, imipramine, intermittent catheterization)

Related Topics
Cranial Nerve Lesions (p. 344)
Orthostatic Hypotension (p. 354)

Dementia

See DEMENTIA (p. 429)

Delirium

See DELIRIUM (p. 432)

Seizures

NEJM 2008 359:2
International League Against Epilepsy (ILAE) Commission 2010
Epilepsia 2014 55:4

DIFFERENTIAL DIAGNOSIS

UNPROVOKED EPILEPTIC SEIZURES

- **PRIMARY EPILEPSIES**—partial (simple, complex, secondarily generalized), generalized (absence, generalized tonic-clonic, myoclonic, atonic, tonic, clonic), unknown (epileptic spasms)
- **STRUCTURAL**—stroke (infarction), head trauma, brain tumors, neuro-degenerative disorders
- **INFECTIONS**—encephalitis

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **CONGENITAL**—neuronal migration errors and cortical dysgenesis, vascular malformations

PROVOKED EPILEPTIC SEIZURES

- **DRUGS**—**lowered seizure threshold** (bupropion, theophylline, isoniazide, imipenem, high-dose penicillin, meperidine), **withdrawal** (benzodiazepine, alcohol), **overdoses** (methanol, ethylene glycol,

DIFFERENTIAL DIAGNOSIS (CONT'D)

TCAs), **illicit drug use** (cocaine, amphetamines, LSD)

- **METABOLIC**—hypoglycemia, non-ketotic hyperglycemia, hyponatremia, hypocalcemia, uremia, hypoxia (cerebral anoxia), hyperthyroidism
- **INFECTIONS**—meningitis, HSV encephalitis, febrile seizures
- **OTHERS**—arrhythmia, acute intermittent porphyria
- **STRUCTURAL** (**USUALLY WITHIN 1–2 WEEKS**)—brain tumors, stroke, head trauma

PSYCHOGENIC NON-EPILEPTIC (PSEUDOSEIZURES)—stressful psychological conflicts, major emotional trauma

OTHER SEIZURE MIMICS—syncope, TIA, migraine, benign positional vertigo, hypoglycemia, sleep disorders (sleep apnea, narcolepsy/cataplexy, night terrors, nightmares, nocturnal myoclonus), periodic paralysis, breath-holding spells

PATHOPHYSIOLOGY

TERMS

- **GENERALIZED**—engaging cortex bilaterally. Loss of consciousness
- **FOCAL WITHOUT IMPAIRMENT OF CONSCIOUSNESS OR AWARENESS**—originating in one hemisphere. Possible motor, sensory, autonomic, or psychic symptoms with sparing of consciousness/awareness. (Roughly corresponds to "simple partial seizure" under old classification)
- **FOCAL DYSCOGNITIVE**—originating in one hemisphere. Possible motor, sensory, autonomic, or psychic symptoms with impaired consciousness/awareness. (Roughly corresponds to "complex partial seizure" under old classification)

PATHOPHYSIOLOGY (CONT'D)

- **FOCAL EVOLVING TO BILATERAL CONVULSIVE SEIZURE**—originating in one hemisphere but evolving to engage cortex bilaterally. (Replaces "secondarily generalized seizure" under old classification)
- **CLONIC**—jerky contractions, rhythmic
- **TONIC**—muscle stiffening
- **EPILEPSY**—any of 1 of 3 criteria: ≥2 unprovoked seizures >24 h apart; 1 unprovoked seizure with probability of another seizure ≥60% over next 10 years (e.g. presence of structural lesion associated with high risk for seizure recurrence); or, diagnosis of epilepsy syndrome
- **STATUS EPILEPTICUS**—≥5 min of continuous seizure activity, or ≥2 discrete seizures without complete recovery of consciouness in between events

TYPES OF EPILEPSIES

- **LOCALIZATION RELATED**—frontal lobe, temporal lobe, parietal lobe, occipital lobe
- **GENERALIZED**—juvenile absence epilepsy, juvenile myoclonic epilepsy, infantile spasms

COMPLICATIONS OF SEIZURES—seizure related injuries (see Medical Fitness to Drive, p. 490), aspiration pneumonia, neurogenic pulmonary edema, hypoxic brain injury, cardiac injury, rhabdomyolysis (acute renal failure, hyperkalemia), lactic acidosis, sudden unexpected death in epilepsy (SUDEP)

CLINICAL FEATURES

HISTORY—when was first seizure, prodrome, aura, ictal symptoms, postictal period, diurnal variation, history suggestive of missed seizure (e.g. waking up with sore muscles, blood in the mouth, or urinary incontinence), precipitants (e.g. sleep deprivation, skipped meals, stress, menses, alcohol, missed medications, medication withdrawal), maximum seizure-free period, seizure types, related injuries, driving and employment

DISTINGUISHING FEATURES BETWEEN SEIZURES AND SYNCOPE

	Generalized seizures	Vasovagal syncope
Past history	Seizures, head injury, stroke, tumor	No strong history
Pre-event	Awake or sleep	Usually upright
	No warning	Usually warning
	Aura	Lightheaded
Event	Vocalization at onset	No vocalization
	Tonic–clonic convulsions	Occasional myoclonic movements, hypotonia
	Cyanotic/gray	Pale
	Incontinence frequent	Incontinence occasionally
	Tongue biting (side)	Tongue biting rare (tip)
	Frequent injuries (fall on face, #, dislocations)	Less commonly injured
	Longer ↓ level of consciousness	Short ↓ level of consciousness
Post-event	Confused, tired, sleepy, post-ictal Todd's paralysis	Alert
	Muscle ache	Diaphoretic

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, Ca, Mg, PO_4, AST, ALT, ALP, bilirubin, albumin, CK, troponin, TSH, INR, PTT, prolactin (acute increase 10–20 min after generalized tonic clonic seizures, low sens)
- **IMAGING**—CT head, MRI head
- **EEG ± SLEEP DEPREIVATION**—for unprovoked or recurrent seizures (best done within 24 h of seizure onset). Consider also sleep deprived EEG to increase the yield of detecting epileptiform activity/focal abnormality

SPECIAL

- **CXR**—if suspect aspiration
- **LUMBAR PUNCTURE**—if suspect meningitis/encephalitis

DIAGNOSTIC ISSUES

AURA—focal seizure with subjective sensory or psychic phenomenon

JACKSONIAN MARCH—focal motor seizure of primary motor cortex will produce clonic activity in contralateral side of the body. Rhythmic activity spreads to adjacent areas (e.g. fingers to wrists to arms)

TODD'S PARALYSIS—hemiparesis or hemiplegia following a seizure, suggests focal onset

ELECTROENCEPHALOGRAM (EEG)

- **DIAGNOSTIC**—useful for epilepsy (sens 40–50%, high spc), metabolic and toxic encephalopathies, herpes encephalitis, subacute sclerosing panencephalitis, and prion diseases such as Creutzfeldt–Jakob disease
- **PROGNOSTIC**—useful for anoxic brain injury (burst suppression, alpha coma, and electrocerebral silence suggests very poor prognosis)

MANAGEMENT

STATUS EPILEPTICUS—**ABC**, O_2, IV, **stat investigations** (ABG, CBCD, lytes, Cr, glucose, Mg, Ca, PO_4, toxic screen, antiepileptic drug level), *glucose* if hypoglycemia (*thiamine* 100 mg IV, 50% *dextrose* 50 mL IV), **first line** (*lorazepam* 2 mg q1–3 min IV push, consider rectal diazepam if no IV access), **second line** (*phenytoin* 20 mg/kg IV, no faster than 50 mg/min, start continuous monitor), **third line** (*midazolam* 0.05–0.3 mg/kg over 20–30 s, repeat PRN), **fourth line** (anesthetic doses of *propofol* 50–100 mg IV bolus, need to intubate). Note: phenytoin and benzodiazepines are incompatible in IV tubing and will precipitate if infused in same line. Use separate IV sites. See p. 113 for treatment of rhabdomyolysis

MANAGEMENT (CONT'D)

ACUTE SEIZURE CONTROL—**benzodiazepines** (*lorazepam* 1 mg IV/SL PRN, up to a total dose of 0.1 mg/kg. *Diazepam* 10 mg PO q6h and 5 mg PO q2h PRN). **Antiepileptic** (*fosphenytoin* 20 mg/kg IV, *phenytoin* 300 mg IV over 10 min, phenobarbital, carbamazepine, valproate). *If* **alcohol withdrawal** (add *thiamine* 100 mg IV/PO daily, *multi-vitamin* 1 tab IV/PO daily)

LONG-TERM MANAGEMENT—*valproic acid* 200–500 mg or 10–15 mg/kg PO daily, increase dose by 250–500 mg/week, typical daily dose is 750–2000 mg; *lamotrigine* 25 mg PO daily, increase dose by 25 mg/week, typical daily dose is 100–400 mg; *topiramate* 25–50 mg PO daily, increase by 25–50 mg/week, typical daily dose is 200–400 mg; *levetiracetam* 250–500 mg PO daily, increase dose by 250–500 mg/week, typical daily dose is 1000–3000 mg; *carbamazepine* 200 mg PO daily, increase by 200 mg every 3 days, typical daily dose is 400–800 mg; *phenytoin* 3–5 mg/kg PO daily (loading dose may be given for quicker effect), typical daily dose is 200–400 mg; *gabapentin* 300 mg daily-BID, increase dose by 300–600 mg/week, typical daily dose is 1800–3600 mg; *pregabalin* 75–150 mg PO daily, increase dose by 75–150 mg/week, typical daily dose is 150–300 mg

PSYCHOSOCIAL ASPECTS—loss of independence, employment, insurance, self-esteem, and ability to drive

DRIVING ISSUES—recommendations vary from region to region. Check with driving authority for specific restrictions and legal requirements. If single unprovoked seizure, usually no driving restrictions are needed as long as EEG and imaging are normal. If >1 unprovoked seizure, consider 6–12 months of seizure-free interval before reinstating driver's license (varies with jurisdiction). Some places may also restrict driving for 6 months after antiepileptic dose adjustments. More stringent rules may exist for commercial drivers

TREATMENT ISSUES

FIRST TIME SEIZURE—if no structural lesion, no physical findings, and normal EEG, usually do not need to start antiseizure medications. Risk of recurrence after first seizure is 30–60%. Risk after second seizure is 80–90%

ANTIEPILEPTIC CHOICES

- **BROAD-SPECTRUM ANTIEPILEPTIC DRUGS**—in decreasing order of efficacy, include valproic acid, lamotrigine, topiramate, levetiracetam, and zonisamide. These antiepileptic medications

TREATMENT ISSUES (CONT'D)

represent reasonable first-line therapy for most seizure types

- **NARROW-SPECTRUM ANTIEPILEPTIC DRUGS**—include carbamazepine, phenytoin, gabapentin, tiagabine, oxcarbazepine, and pregabalin. These medications are effective against focal seizures with or without secondarily generalized features, but have limited activity against primary generalized seizure disorders (e.g. carbamazpeine may even worsen juvenile myoclonic epilepsy)

	P	C	V	B	L	G	T	E
Tonic-clonic	+	+	1	+	+	±		
Absence			+					1
Status	+			+				
Partial	+	1	+	+		±	+	
Myoclonic			+	+				

Key: *P* phenytoin, *C* carbamazepine, *V* valproate, *B* phenobarbital, *L* lamotrigine, *G* gabapentin, *T* levetiracetam or topiramate, *E* ethosuximide, *1* drug of choice, + possible use, ± adjunct use

STOPPING ANTIEPILEPTICS—consider stopping anticonvulsants after a seizure-free period of 2–5 years. Relapse is 26–63% within 1–2 years after withdrawal. Risk factors for recurrence include abnormal EEG before or during withdrawal, abnormal neurologic findings, frequent seizures before remission, and mental retardation. Be sure to consult local driving regulations with regards to restrictions while undertaking an antiepileptic drug taper

TREATMENT ISSUES (CONT'D)

DRUG- OR TOXIN-INDUCED SEIZURES—top five drug-induced etiologies include isoniazide, theophylline, oral hypoglycemic agents, carbon monoxide, and bupropion. Supportive management for theophylline-induced, carbon monoxide-induced, and bupropion-induced seizures. Treat isoniazide-induced seizures with pyridoxine; hypoglycemic seizures with glucose ± octreotide and glucagon; and carbon monoxide-associated seizures with oxygen (hyperbaric oxygen controversial)

Related Topics
Brain Tumors (p. 335)
Seizures in Pregnancy (p. 476)
Toxicology (p. 114)

Syncope

DIFFERENTIAL DIAGNOSIS

★SVNCOPE★

SITUATIONAL—micturition, defecation, coughing, laughing

VASOVAGAL—painful, emotional stimulus, head turning

NEUROGENIC—vestibular stroke, seizures, autonomic insufficiency

CARDIOGENIC

- **CONDUCTION**—VT, AV block/Stokes–Adams, prolonged QT, carotid sinus hypersensitivity (shaving, tight collars)
- **VALVULAR**—aortic stenosis, mitral stenosis, pulmonary stenosis, tricuspid stenosis
- **VASCULAR**—pulmonary hypertension, pulmonary embolism
- **PERICARDIAL**—tamponade
- **MYOCARDIAL**—myocardial infarction, hypertrophic cardiomyopathy

ORTHOSTATIC

PSYCHOGENIC

ETC—drugs

CLINICAL FEATURES

HISTORY—N&V before collapse, syncope with exertion, seizure features (tongue biting, incontinence, post-collapse disorientation), last meal, history of cardiac disease (arrhythmias, heart failure, ischemic heart disease, aortic stenosis), previous syncope, seizures, or psychiatric problems, current medications, family history of unexplained syncope or sudden death

PHYSICAL—orthostatic hypotension, irregular or slow-rising pulse, apical-carotid delay, soft or paradoxically split S2, presence of S4, murmurs (particularly aortic stenosis), carotid sinus massage, injuries, decreased level of consciousness, any focal neurological signs

OVERALL—history is most useful for diagnosis especially from reliable witness, revealing causes in ~45% of cases. Despite different investigations, cause of syncope remains undiagnosed in 50%. Mostly benign (e.g. vasovagal), but 1-year mortality up to 30% in high-risk patients. Highest diagnostic yield from postural BP measurement. Lowest diagnostic yields from head CT, carotid ultrasound, EEG, and cardiac enzymes

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, Cr/urea, CK, troponin
- **IMAGING**—CXR, echocardiogram, carotid dopplers, CT head
- **OTHERS**—ECG, 24 h Holter

SPECIAL

- **EEG**—if suspect seizures
- **STRESS TEST**
- **TILT TABLE TEST**—to confirm vasovagal syncope

MANAGEMENT

ACUTE—ABC, O_2, IV
TREAT UNDERLYING CAUSE

TREATMENT ISSUES

SAN FRANCISCO SYNCOPE RULE—prospectively validated to improve prediction of serious outcomes in patients with syncope and to guide admission decisions. If patient has any of 5 risk factors ★**CHESS**★ **C**HF history, **H**ct <30, **E**CG abnormality, **S**BP <90 mmHg, or **S**hortness of breath, then admit for further workup. Sensitivity 96%, reduces admissions by 10%

Arch Intern Med 2009 169:14

SPECIFIC ENTITIES

REFLEX SYNCOPE—consists of situational syncope, vasovagal syncope, and carotid sinus syndrome

NEUROCARDIOGENIC (VASOVAGAL) SYNCOPE

- **PATHOPHYSIOLOGY**—prolonged standing, vigorous exercise, emotional distress, severe pain → excessive peripheral venous pooling → decreased venous return → compensation with cardiac hypercontractile state → activation of mechanoreceptors (and this is seen by brain as hypertension-like) causing paradoxical reflex bradycardia and drop in peripheral vascular resistance → decreased output to brain → syncope
- **CLINICAL FEATURES**—pre-syncope symptoms may include weakness, light-headedness, diaphoresis, visual blurring, headache, nausea, and feeling warm or cold. Syncope lasts about 30 s to 5 min. Recovery is rapid with minimal postictal state
- **DIAGNOSIS**—tilt-table test (spc 90%), implantable loop recorders
- **TREATMENTS**—lie down if pre-syncope, adequate fluids and salt intake, SSRI (*paroxetine* 20 mg PO daily), vasoconstrictor (*midodrine* 2.5–10 mg PO TID), permanent cardiac pacing if recurrent

NEJM 2005 352:10

SITUATIONAL SYNCOPE—similar to vasovagal syncope in pathophysiology, but due to mechanoreceptors in esophagus, lungs, bladder, and rectum triggered by coughing, swallowing, urination, and defecation, respectively

NEUROGENIC ORTHOSTATIC HYPOTENSION

- **PATHOPHYSIOLOGY**—standing leads to pooling of blood (500–1000 mL) in legs → decreased venous return to right atrium → decreased cardiac output. Normally, this triggers the autonomic response via baroreceptors in carotid sinus and aortic arch, resulting in increased peripheral vascular resistance and cardiac output. In orthostatic hypotension, this response is dampened or lost with autonomic failure, leading to hypoperfusion of various organs → lightheadedness, dizziness, syncope, weakness, fatigue, angina, orthostatic dyspnea. Typically happens in older individuals and exacerbated by prolonged standing, strenuous exercises, high temperature, and meals
- **CAUSES**—see autonomic neuropathy for more details (p. 371)
- **CLINICAL FEATURES**—pre-syncope symptoms may include weakness, light-headedness, diaphoresis, visual blurring, headache, nausea and feeling warm or cold. Syncope lasts about 30 s to 5 min. Recovery is rapid with minimal postictal state
- **DIAGNOSIS**—SBP drop of ≥20 mmHg or DBP drop of ≥10 mmHg during first 3 min of standing, or a head-up tilt on tilt table. Autonomic failure may be assessed by heart rate variability testing
- **TREATMENTS**—gradual staged movements with postural changes, exercises, increase salt/fluid intake, elastic stockings, and minimize antihypertensive medication use. Medications include *fludrocortisone* 0.05–0.1 mg PO daily, midodrine, pseudoephedrine, ephedrine, and potentially pyridostigmine

NEJM 2008 358:6

Related Topics
Arrhythmia (p. 45)
Dizziness (p. 357)
Falls (p. 434)
Stroke (p. 337)
Valvular Heart Disease (p. 54)

Migraine Headaches

NEJM 2002 346:4; NEJM 2006 354:2

DIFFERENTIAL DIAGNOSIS OF HEADACHES

PRIMARY—migraine, cluster, tension, medication overuse
INFECTIONS—meningitis, encephalitis
STRUCTURAL—**hemorrhage** (subarachnoid, epidural, subdural, intracerebral), **thrombosis** (ischemic stroke, cerebral vein), **tumor**, **trauma**

DIFFERENTIAL DIAGNOSIS OF HEADACHES (CONT'D)

OTHERS—sinusitis, temporal arteritis, pseudotumor cerebri, trigeminal neuralgia, pituitary apoplexy

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT WITH HEADACHE HAVE A MIGRAINE OR NEED NEUROIMAGING?

★POUND★ CRITERIA—**P**ulsating, duration of 4–72 h**O**urs, **U**nilateral, **N**ausea, **D**isabling (LR+ 24 if 4 criteria, LR+ 3.5 if 3 criteria, LR+ 0.41 if ≤2 criteria)

	LR+	LR–
Chronic headache features suggestive of serious intracranial abnormality requiring neuroimaging		
Cluster-type headache	11	0.95
Abnormal findings on neurologic examination	5.3	0.71
Undefined headache	3.8	0.66
Headache with aura	3.2	0.51
Headache aggravated by exertion or a Valsalva-like maneuver	2.3	0.7
Headache with vomiting	1.8	0.47

APPROACH—"the presence of 4 simple historical features can accurately diagnose migraine. Headaches may be classified as new headache, acute thunderclap headache, or chronic headache. Neuroimaging may be done for new headaches at the discretion of physician. All acute thunderclap headaches should be investigated with neuroimaging and lumbar puncture. Chronic headaches with high risk features above should be investigated with neuroimaging. No clinical features were useful in ruling out significant pathologic conditions"

JAMA 2006 296:10

CLINICAL FEATURES (CONT'D)

ALARM SYMPTOMS (suggesting secondary causes)—**★SNOOP2★**

- **SYSTEMIC SYMPTOMS OR ILLNESS**—constitutional symptoms (fever, weight loss, malaise, myalgias, scalp tenderness, jaw claudication), malignancy, HIV
- **NEUROLOGICAL SYMPTOMS OR SIGNS**—confusion, decreased level of alertness, meningismus, papilledema, seizures
- **ONSET OF "THUNDERCLAP HEADACHE"**—maximal intensity within first 60 s
- **OLDER AGE**—new onset after age 50
- **POSTURAL CHANGE**—precipitated by Valsalva maneuver or exertion
- **PROGRESSIVE WORSENING**—rapidly over days to months, or worsening of a previously stable/typical headache

HISTORY—temporal factors such as onset and duration of each episode as well as frequency are particularly important in making the diagnosis.

CLINICAL FEATURES (CONT'D)

Characterize headaches (location, nature, intensity, radiation, alleviation, and aggravation), precipitants (stress, food, physical activity), and any associated neurological symptoms. Consider past medical history, current medications (especially headache medications). Consider temporal arteritis (jaw claudication, visual changes, scalp tenderness) in the elderly, history of PMR.

PHYSICAL—vitals. Neurological examination including visual fields and fundoscopy. Remember to check temporal arteries in the elderly

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, ESR (temporal arteritis), INR, PTT
- **IMAGING**—CT head, MRI head

SPECIAL

- **LUMBAR PUNCTURE**

DIAGNOSTIC ISSUES

INTERNATIONAL HEADACHE SOCIETY MIGRAINE CRITERIA (ICHD-II)

1. At least 5 attacks
2. Episodic attacks lasting 4–72 h (untreated or unsuccessfully treated)
3. Any 2 of unilateral pain, pulsating, moderate or severe intensity, pain aggravated by or causing avoidance of routine physical activity
4. Any 1 of N&V, photophobia, and phonophobia
5. Exclude secondary causes

MANAGEMENT OF MIGRAINE HEADACHES

SYMPTOM CONTROL—**regularity in life activities** (sleep, eat, exercise), **first-line agents** (*acetaminophen* 650 mg PO q4h, *ibuprofen* 400–800 mg PO q6h), **second-line agents** (*dihydroergotamine* 0.5–1 mg IV, *ketorolac* 30 mg IV, *sumatriptan* 50 mg PO or 6 mg SC, naratriptan, rizatriptan, eletriptan, zolmitriptan), **antiemetics**/**dopamine antagonists** (*metoclopramide* 10 mg IV, *prochlorperazine* 10 mg IV + 500 mL NS). Consider adding *dexamethasone* 10–25 mg IV or IM × 1 with standard acute migraine therapy for patients in ER or clinic to reduce rate of early headache recurrence

PROPHYLAXIS—indicated if patient has ≥3 attacks per month, severe prolonged attacks, or when poor response to abortive medications. Choices include **tricyclic antidepressants** (*amitriptyline* 25–300 mg PO qhs, *desipramine* 25–200 mg PO qhs, nortriptyline), **β-blockers** (atenolol, propranolol, metoprolol, and nadolol), **anticonvulsants** (valproic acid, topirimate, gabapentin), **calcium channel blockers** (verapamil), **botulinum toxin**

SPECIFIC ENTITIES

CHRONIC DAILY HEADACHES—any headaches >15 days per month for >3 months. Risk factors include obesity, history of frequent headache (>1 per week), caffeine consumption, and overuse of acute headache medications (analgesics, ergots, triptans). Common forms of chronic daily headaches include transformed migraine (migraine symptoms with chronic daily features), medication overuse headache (use of headache medications >15 days per month), and chronic tension-type headache

TENSION HEADACHES—chronic daily, mild-to-moderately severe, bilateral (band like), usually stress related. Treatments include stress reduction, tricyclic antidepressants for prophylaxis, and pain control PRN

CLUSTER HEADACHES—chronic daily headaches with up to 8× 1-h attacks each day lasting 4–8 weeks per episode, with 1–3 episodes per year. Extremely severe, mostly periorbital or temporal. Associated with autonomic symptoms (tearing, rhinorrhea), Horner syndrome (Horton headache), and motor restlessness

HYPNIC HEADACHES—chronic daily (only happens during sleep), moderately severe, bilateral

HEMICRANIA CONTINUA—constant exacerbations of severe headaches ("ice-pick" pain), unilateral, cranial autonomic symptoms. By definition, responsive to indomethacin

PAROXYSMAL HEMICRANIA—similar to cluster headaches except that attacks are more frequent (>5x and up to 24× per day) and are shorter (8–25 min). By definition, responsive to indomethacin

PSEUDOTUMOR CEREBRI (idiopathic intracranial hypertension)

- **PATHOPHYSIOLOGY**—idiopathic ↑ in intracranial pressure predominantly in obese women of child-bearing age → headache worse upon awakening and with change of position, associated with transient visual changes, papilledema and sometimes sixth nerve palsy
- **DIAGNOSIS**—MRI/MRV (to exclude other causes such as cerebral vein thrombosis), lumbar puncture with ↑ opening pressure (>200 mmH_2O in non-obese, >250 mmH_2O in obese patients, otherwise normal CSF chemistry)
- **TREATMENTS**—weight loss, NSAIDs for pain, furosemide, *acetazolamide* 250 mg PO QID (medical management should be combined with surgical management if visual loss), lumboperitoneal shunting, optic nerve sheath fenestration, serial neuro-ophthalmologist follow-up

Meningitis

See MENINGITIS (p. 269)

Dizziness and Vertigo

DIFFERENTIAL DIAGNOSIS

VERTIGO

- **CENTRAL**—vertebrobasilar insufficiency, vertiginous migraine (9%), multiple sclerosis, cerebellopontine angle tumor, cerebellar hemorrhage, subclavian steal
- **PERIPHERAL**—benign positional vertigo (30%), acute labyrinthitis/vestibular neuronitis (3%), acute recurrent peripheral vestibulopathy, Meniere's disease (6%), cholesteatoma, drugs (aminoglycoside, phenytoin), acoustic neuroma, herpes zoster oticus, deep sea diving

DIFFERENTIAL DIAGNOSIS (CONT'D)

SYNCOPE/PRE-SYNCOPE/ORTHOSTATIC HYPOTENSION—see SYNCOPE (p. 353)

IMBALANCE—spastic gait (infarction), apraxic gait (normal pressure hydrocephalus, frontal lobe dementia, Alzheimer's), ataxia gait (cerebellar disorder), shuffling gait (Parkinson's disease), sensory ataxia gait (decreased proprioception), Trendelenburg gait (proximal muscle weakness), steppage gait (impaired dorsiflexion)

VAGUE DIZZINESS/LIGHT-HEADEDNESS—panic attacks, hyperventilation, multisensory dizziness

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE VERTIGO?

	PPV	NPV	LR+	LR–
History				
Positive head-hanging maneuver plus either vertigo or vomiting predict peripheral vertigo	85%	68%	7.6	0.6
Absence of vertigo or age >69 or presence of neurological deficit predict serious causes of dizziness	40%	88%	1.5	0.3

APPROACH—"in patients with suspected vertigo, ask whether they have dizziness when changing body position (rolling over in bed, looking up at the ceiling, or bending over to tie shoelaces) and perform a headhanging maneuver to check for positional nystagmus. In combination with other data (including a brief neurological examination) in an emergency department setting, the absence of positional nystagmus can be useful in identifying serious causes of dizziness"

JAMA 1994 271:5

CLINICAL FEATURES (CONT'D)

HISTORY—distinguish between vertigo, lightheadedness, pre-syncope, and imbalance. Characterize duration of each episode and frequency (most important), direction of spin, precipitants, aggravations (standing or other positions), alleviations, any associated neurologic symptoms (particularly hearing changes, visual changes, facial sensory change, bulbar symptoms, headache), N&V, falls, past medical history (stroke, malignancy), medications (aminoglycosides)

PHYSICAL—postural vitals. Complete neurological examination, particularly focusing on nystagmus, hearing, dysmetria, and gait.

CLINICAL FEATURES (CONT'D)

Examine for BPPV with Dix–Hallpike maneuver (predicts responsiveness to canalith repositioning)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, TSH
- **IMAGING**—CT head, MRI head

SPECIAL

- **ELECTRONYSTAGMOGRAPHY WITH CALORIC TESTING**
- **SYNCOPE WORKUP**—ECG, 24 h Holter
- **AUDIOMETRY**

DIAGNOSTIC ISSUES

DISTINGUISHING BETWEEN CENTRAL AND PERIPHERAL VERTIGO

	Central	Peripheral
Onset	More gradual	More sudden
Nystagmus	Purely horizontal, vertical, rotational	Usually horizontal and rotational
	Not inhibited by fixation onto object	Inhibited by fixation of eyes onto object
	Persists for a longer period	Shorter duration
N&V	Varies	More severe
Others	Severe imbalance	Tullio's phenomenon (nystagmus and vertigo caused by loud noises at a particular frequency)
	Other non-auditory cranial nerve symptoms usually present	Tinnitus, hearing loss

DIAGNOSTIC ISSUES (CONT'D)

MRI HEAD—used to rule out acoustic neuroma, posterior fossa tumors, stroke, or demyelinating disease. Indications include unexplained asymmetric sensorineural hearing loss with retrocochlear features, sudden and unexplained complete unilateral vestibular loss, or other brainstem signs or symptoms

Related Topic
Syncope (p. 353)

MANAGEMENT

SYMPTOM CONTROL—**benzodiazepines** (*diazepam* 2–10 mg IV), **anticholinergic** (*meclizine* 25 mg PO q8–12 h, *dimenhydrinate* 25–50 mg PO q4h, *diphenhydramine* 25–50 mg PO q4h, *promethazine* 25 mg PO q4–6 h), **histamine analogue** (*betahistine* 8–16 mg PO TID for Meniere's disease)

SPECIFIC ENTITIES

BENIGN PAROXYSMAL POSITIONAL VERTIGO

- **PATHOPHYSIOLOGY**—calcium debris in posterior semicircular canal (canalithiasis)
- **CLINICAL FEATURES**—vertigo (typically <1 min/episode, multiple episodes per day) usually precipitated by change in position, nystagmus, and sometimes N&V. No hearing loss or focal deficits
- **DIAGNOSIS**—Dix–Hallpike maneuver (examiner stands at head of bed; patient is supported and quickly lowered into supine position with head ~30° below level of examining table and rotated ~30° to side; examiner observes for induced nystagmus, reproduced symptoms; repeat with rotation in opposite direction)
- **TREATMENTS**—may improve with canalith repositioning maneuvers (e.g. Epley maneuver). Usually self-limited and resolves over months

MIGRAINOUS VERTIGO

- **CLINICAL FEATURES**—vertigo (typically minutes to hours, sporadically), photophobia, sonophobia, headache

BRAIN-STEM/LABYRINTH TIA

- **PATHOPHYSIOLOGY**—embolic/thrombotic phenomenon
- **CLINICAL FEATURES**—vertigo (minutes to hours, sporadically), usually other neurological deficits such as facial sensory loss, diplopia, dysarthria, dysphagia, weakness, or numbness
- **DIAGNOSIS**—CT head, MRI head

MÉNIÈRE'S DISEASE

- **PATHOPHYSIOLOGY**—endolymphatic hydrops → distension of the labyrinthine system, compressing the perilymphatic spaces
- **CLINICAL FEATURES**—vertigo (typically hours, sporadically), N&V, sensorineural hearing loss, tinnitus and aural fullness
- **DIAGNOSIS**—2 spontaneous episodes of vertigo (>20 min each), audiometric confirmation of sensorineural hearing loss, tinnitus/aural fullness
- **TREATMENTS**—betahistine, hearing aid use, intracochlear gentamicin injection

ACUTE LABYRINTHITIS/VESTIBULAR NEURONITIS

- **PATHOPHYSIOLOGY**—labyrinthitis/vestibular neuronitis secondary to viral infection
- **CLINICAL FEATURES**—vertigo (typically days, sporadically) that may be precipitated by change in position (labyrinthitis) or spontaneous (vestibular neuronitis), severe N&V

Hearing Impairment

DIFFERENTIAL DIAGNOSIS

SENSORINEURAL (inner ear to cortex)—**CVA**, **presbycusis**, **multiple sclerosis**, **Meniere's disease**, **trauma** (noise exposure, barotrauma, penetrating trauma), **tumor** (acoustic neuroma, meningioma), **infectious** (viral cochleitis, meningitis, syphilis), **congenital** (viral infections, malformations, hereditary hearing loss), **iatrogenic** (5-FU, bleomycin, nitrogen mustard, erythromycin, vancomycin, tetracycline, aminoglycoside, ASA, otologic surgery), **autoimmune**, **thyrotoxicosis**

CONDUCTIVE

- **MIDDLE EAR**—**trauma** (tympanic membrane perforation, temporal bone trauma), **tumor** (cholesteatoma, otosclerosis, glomus tumors), **infectious** (otitis media), **congenital** (congenital atresia, ossicular chain malformation)
- **OUTER EAR**—**trauma** (canal), **tumor** (squamous cell cancer, exostosis, osteoma), **infectious** (external otitis), **congenital** (congenital microtia, atresia), **others** (cerumen, psoriasis)

MIXED—conductive and sensorineural hearing loss

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE HEARING IMPAIRMENT?

	LR+	LR–
History		
Asking patients whether they have hearing impairment	2.5	0.13
Hearing handicap inventory for the elderly (screening version) score of ≥8	3.8	0.38
Physical		
Inability to perceive whispering	6.1	0.03
Weber test	1.6–1.7	0.70–0.76
Rinne test	2.7–62	0.01–0.85
Investigations		
Not passing the audioscope test	2.4	0.07

APPROACH—"elderly individuals who acknowledge they have hearing impairment require audiometry, while those who reply no should be screened with the whispered voice test. Individuals who perceive the whispered voice require no further testing, while those unable to perceive the voice require audiometry. The Weber and Rinne tests should not be used for general screening"

JAMA 2006 295:4

RINNE TEST—256 Hz tuning fork on mastoid process, when vibration no longer heard, placed in line with external meatus. If can still hear (air conduction > bone conduction), either normal or sensorineural loss on that side (equally affected bone and air conduction). If cannot hear any more (bone conduction > air conduction), conductive hearing loss on that side. Note: positive Rinne test refers to *normal* air conduction > bone conduction (paradoxical terminology)

WEBER TEST—256 Hz tuning fork on bridge of forehead. Normal = equal on both sides. If hear louder on one side, either that side has conductive loss or opposite side has sensorineural loss

	Weber	Rinne
Conductive loss		
Good ear	Quieter	AC > BC
Bad ear	Louder	BC > AC
Sensorineural loss		
Good ear	Louder	AC > BC
Bad ear	Quieter	AC > BC

NOTE: *AC* air conduction, *BC* bone conduction

INVESTIGATIONS

BASIC

- **FORMAL AUDIOLOGICAL ASSESSMENT**—formal audiogram, tympanogram, site of lesion testing

SPECIAL

- **IMAGING**—MRI/CT of posterior fossa/internal auditory canal
- **REVERSIBLE CAUSES WORKUP**—TSH, VDRL

MANAGEMENT

SYMPTOM CONTROL—**speak in front of patient** so they can read lips (do not speak too loudly as this changes lip movement). If they do not understand, restructure sentence. Do not just repeat. **Write. Hearing amplifier** (stethoscope, electronic)

TREAT UNDERLYING CAUSE—**audiology** and/or **ENT** consult

Myasthenia Gravis

DIFFERENTIAL DIAGNOSIS OF PTOSIS

MECHANICAL—aponeurotic ptosis (spontaneous dehiscence of the levator aponeurosis), eyelid infections, eyelid tumors

NEUROMUSCULAR—third nerve palsy (usually unilateral), Horner's syndrome (usually unilateral), myasthenia gravis (bilateral or unilateral), botulism (usually bilateral), Lambert-Eaton syndrome, myotonic dystrophy (usually bilateral)

PATHOPHYSIOLOGY

ANTIBODY AGAINST POST-SYNAPTIC ACETYLCHOLINE RECEPTOR—leads to decreased neurotransmission and muscle weakness (ocular, bulbar, and skeletal)

ASSOCIATIONS—thymic diseases (hyperplasia, thymoma, carcinoma) can be found in 75% of patients with myasthenia gravis. Other associations include hyperthyroidism, small cell lung cancer, Hodgkin's lymphoma, SLE, and rheumatoid arthritis. Key differential diagnoses include depression, ALS, and Lambert–Eaton syndrome

CLINICAL FEATURES

HISTORY—ptosis (classically fluctuating and asymmetric in myasthenia gravis), diplopia, bulbar weakness (slurred speech, hoarseness, difficulty chewing and swallowing), limb weakness, shortness of breath, symptoms better with rest and worse with prolonged use, past medical history (malignancy, trauma), medications

PHYSICAL—vitals, pulmonary examination, measure palpebral fissure at rest and after sustained upward gaze for 30 s, extraocular eye movements, orbicularis oculi weakness (cannot bury eye lashes). Peek sign is positive when palpebral fissure can be seen after patient tries to gently close the eye lids), voice changes, assess for weakness of neck flexor, deltoids, hip flexors, finger/wrist extensors, and foot dorsiflexors with repeated challenges. Sensory examination should be normal and reflexes should demonstrate fatigability

SPECIAL TESTS FOR MYASTHENIA GRAVIS—**ice test** (improvement of ptosis with palpebral fissure increase of 2 mm after applying ice over eyelid for 2 min), **sleep test** (improvement of ptosis with palpebral fissure increase of 2 mm after resting in dark room for 30 min), **curtain sign**, **lid twitch sign**, **cover–uncover test** (examiner covers one eye as patient fixates on a distant object. Observe for deviation of the uncovered eye during lateral and then upward gazing. With extraocular weakness, the uncovered eye will drift)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE MYASTHENIA GRAVIS?

	LR+	LR–
History		
Food in mouth after swallowing	13	0.70
Speech becoming unintelligible during prolonged speaking	4.5	0.61
Physical		
Peek sign	30	0.88
Ice test	24	0.16
Sleep test	53	0.01
Special tests		
Edrophonium test	15	0.11

APPROACH—"the presence of speech becoming unintelligible after prolonged periods and peek sign may be useful in confirming the diagnosis of myasthenia gravis, though their absence does not rule it out. The ice test, sleep test, and response to anticholinesterase agents (especially the edrophonium test) are useful in confirming the diagnosis, and reduce the likelihood when results are negative. A positive test result should prompt acetylcholine receptor antibody testing and specialist referral for electrophysiologic tests and should help confirm the diagnosis in patients who have negative results for the acetylcholine receptor antibody panel"

JAMA 2005 293:15

CLINICAL FEATURES (CONT'D)

DISTINGUISHING FEATURES BETWEEN HORNER'S SYNDROME AND THIRD NERVE PALSY

	Horner's syndrome	Third nerve palsy
Ptosis	Partial. Never complete	Partial or complete
Pupil size	Constricted	Dilated
Pupil asymmetry	Worse in darkness	Worse in light
Pupil reflex	Normal	Sluggish or absent
Others	Anhydrosis Enophthalmos Absent ciliospinal reflex Heterochromia (congenital)	Affected eye downward and outward

INVESTIGATIONS

BASIC

- **LABS**—TSH, ANA, RF
- **IMAGING**—CT chest (thymoma, malignancy), CT/MR head (if third nerve palsy)

SPECIAL

- **EDROPHONIUM (TENSILON) TEST**—injection of acetylcholinesterase inhibitor, improvement may be detected in 30 s and lasts <5 min
- **ANTIBODIES**—anti-acetylcholine receptor antibody (sens 80–90%, very high spc), muscle-specific receptor tyrosine kinase antibody
- **SINGLE FIBER EMG WITH/WITHOUT REPETITIVE STIMULATION**

MANAGEMENT OF MYASTHENIA GRAVIS

MYASTHENIA GRAVIS—*pyridostigmine* 30 mg PO q3–6 h. Thymectomy (controversial if no thymoma). Other treatments include corticosteroids, azathioprine, cyclosporine, mycophenolate, plasmapheresis, IVIG

MYASTHENIC CRISIS—ICU admission, treat any precipitating infection, discontinue any anticholinesterase agents, correct electrolyte abnormality (careful with magnesium replacement as can precipitate crisis), monitor respiratory status, and

MANAGEMENT OF MYASTHENIA GRAVIS (CONT'D)

intubate if FVC <15 to 20 mL/kg or MIP < −25 to −30 cmH_2O, plasmapheresis

SPECIFIC ENTITIES

LAMBERT–EATON SYNDROME (LES)

- **PATHOPHYSIOLOGY**—antibody against presynaptic voltage-gated calcium channels. Small cell lung cancer is found in 50–70% of patients with Lambert–Eaton syndrome
- **CLINICAL FEATURES**—proximal muscle weakness (hip girdle and shoulder. Less likely bulbar, but ptosis still possible. Hyporeflexia that improves with repeated effort (facilitation), autonomic symptoms (dry mouth, impotence). Symptoms worse in morning and improve during day/exercise
- **DIAGNOSIS**—nerve conduction studies with repetitive nerve stimulation. CXR to look for malignancy
- **TREATMENTS**—treat underlying malignancy, plasma exchange, IVIG

Related Topics
Horner's Syndrome (p. 16)
Thymoma (p. 207)

Ataxia

DIFFERENTIAL DIAGNOSIS

CEREBELLAR ATAXIA

- **HEMISPHERES/POSTERIOR LOBE SYNDROME** (intention tremor, dysmetria, dysdiadochokinesia, slurred speech)
- **SUPERIOR VERMIS/ANTERIOR LOBE SYNDROME** (truncal and gait ataxia)—alcoholism and thiamine deficiency

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **FLOCCULONODULAR LOBE SYNDROME** (dysequilibrium, vertigo, and nystagmus)—brain tumors (medulloblastoma)

SENSORY ATAXIA (proprioceptive changes)—tabes dorsalis, peripheral neuropathy

VESTIBULAR ATAXIA (may be associated with vertigo)

THALAMIC ATAXIA (pyramidal tract signs)

CLINICAL FEATURES

DISTINGUISHING FEATURES BETWEEN CEREBELLAR DISORDER AND TABES DORSALIS
(see p. 272)

	Cerebellar ataxia	Tabes dorsalis
History	Speech Δ	Sensory Δ
	Incoordination	Bowel/bladder Δ
	Gait difficulties	Impotence, pain
Inspection	Normal cognition	Dementia if neurosyphilis
	Ataxic speech	
H&N	Nystagmus	Argyll Robertson pupils
	Scanning speech	Optic atrophy
	Explosive speech	
Motor	Hypotonia	Normal tone
	Dysmetria, dysdiadochokinesia, heel-shin test	Heel-shin test
	Pendular reflexes	Absent reflexes (Westphal's sign)
		Extensor plantar
Sensory	Normal	↓ vibration and proprioception
Gait	Truncal ataxia	Slap foot gait
	Wide-based gait	Wide-based gait
Romberg	Positive with eyes closed and open	Positive with eyes closed only

CLINICAL FEATURES (CONT'D)

HISTORY—characterize ataxia (truncal or limb, timing, progressive), speech changes, vision changes, incoordination, falls, headaches, nausea and vomiting, weight loss, past medical history (alcohol use, stroke, multiple sclerosis, malignancy, Wilson's disease), medications, family history

PHYSICAL—nystagmus, ataxic speech ("British constitution," explosive in volume, scanning), hypotonia, dysdiadochokinesia, finger-to-nose test (dysmetria), heel-shin test, pendular reflex, wide based stance, ataxic gait (wide based and staggering), rebound (outstretched arms swing easily when pushed), pronator drift (upward), truncal ataxia (Romberg's test shows unsteadiness with eyes both open and closed)

INVESTIGATIONS

IMAGING—CT/MR head

MANAGEMENT

TREAT UNDERLYING CAUSE

Subacute Combined Degeneration

See VITAMIN B12 DEFICIENCY (p. 459)

Parkinson's Disease

CLASSIFICATION OF MOVEMENT DISORDERS

HYPOKINETIC

- **BRADYKINESIA**
- **RIGIDITY**
- **POSTURAL INSTABILITY**
- **PARKINSONIAN SYNDROMES**—constellation of rest tremor, rigidity, bradykinesia, and loss of postural reflexes

CLASSIFICATION OF MOVEMENT DISORDERS (CONT'D)

HYPERKINETIC

- **DYSTONIA/ATHETOSIS**—sustained muscle contraction, causing twisting and repetitive movements/posture
- **TREMOR**—oscillations produced by alternating contractions of reciprocally innervated

CLASSIFICATION OF MOVEMENT DISORDERS (CONT'D)

muscles, e.g. physiological, essential, intention, rest

- **MYOCLONUS**—sudden shock-like muscle contractions, e.g. focal, multifocal, generalized
- **CHOREA/BALLISM**—arrhythmic, rapid, jerky, purposeless movements. Ballismus is large amplitude, proximal chorea, e.g. Huntington's chorea
- **PSEUDOATHETOSIS**—chorea-type movements secondary to sensory loss
- **PAINFUL LEGS AND MOVING TOES**—continuous, stereotyped, flexion–extension, or adduction–abduction movements of toe
- **PERIODIC LEG MOVEMENT OF SLEEP**—nocturnal myoclonus, with repetitive stereotyped extension of big toe
- **RESTLESS LEG SYNDROME**—abnormal sensation in legs, especially at night
- **ALIEN LIMB**—complex non-volitional movements (reaching, grasping)
- **TICS**—rapid, non-rhythmic movement or sound on background of normal activity
- **STEREOTYPY**—tardive dyskinesia
- **AKATHISIA**—motor activity from voluntary effort to relieve uncomfortable sensation, mainly in daytime
- **PHANTOM DYSKINESIA**—amputees
- **HEMIFACIAL SPASM**—unilateral contraction of facial muscles involving eyelids, cheek, and corner of mouth
- **STARTLE DISEASE OR HYPEREKPLEXIA, STIFF-PERSON SYNDROME**—continuous isometric contractions of somatic muscles

PATHOPHYSIOLOGY

PARKINSONISM ★TRAP★—any 2 of **T**remor, **R**igidity, **A**kinesia/bradykinesia, and **P**ostural instability

PATHOPHYSIOLOGY (CONT'D)

Parkinson's disease is primary or idiopathic parkinsonism. Secondary or acquired parkinsonism may be due to head trauma, cerebrovascular disease, drugs (neuroleptics, dopamine receptor antagonists), or hydrocephalus

PARKINSONISM PLUS SYNDROMES—progressive supranuclear palsy, multiple system atrophy, Lewy body dementia, cortico-basal ganglionic degeneration

CLINICAL FEATURES

PHYSICAL EXAMINATION FOR PARKINSON'S DISEASE—resting tremor (4–6 Hz), rigidity, bradykinesia, micrographia, dementia, stare (reduced blink rate), mask face (hypomimia), glabellar tap, sialorrhea, dysarthria, difficulty getting up from chair, postural instability, difficult with heel-to-toe walking, festination, freezing gait, shuffling gait, and *en bloc* turn. Associated with disordered sleep (difficulty turning in bed), constipation, pain, and depression

DISTINGUISHING FEATURES BETWEEN PHYSIOLOGIC AND PSYCHOGENIC MOVEMENT DISORDERS

- **HISTORY**—abrupt onset, static course, spontaneous remissions (inconsistency over time), obvious psychiatric disturbance, multiple somatizations, healthcare worker, pending litigation or compensation, secondary gain
- **PHYSICAL**—inconsistent character of movement (amplitude, frequency, distribution, selective disability), paroxysmal, movements increase with attention or decrease with distraction, ability to trigger or relieve the abnormal movements with unusual or non-physiological interventions, false weakness, false sensory complaints, self-inflicted injuries, deliberate slowness of movements, functional disability out of proportion to exam findings
- **THERAPEUTICS**—unresponsiveness, response to placebo, remission with psychotherapy

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE PARKINSON'S DISEASE?

	LR+	LR–
History		
Tremor	1.4–11	0.24–0.60
Rigidity	1.3–4.5	0.12–0.93
Difficulty rising from chair	1.9–5.2	0.39–0.58
Loss of balance	1.6–6.6	0.29–0.35
Shuffling gait	3.3–15	0.32–0.50
Difficulty opening jars	6.1	0.26
Difficulty turning in bed	13	0.56

CLINICAL FEATURES (CONT'D)

	LR+	LR–
Micrographia	2.8–5.9	0.30–0.44
Physical		
Tremor	1.5	0.47
Rigidity and bradykinesia	4.5	0.12
Rigidity	2.8	0.38
Asymmetry	1.8	0.61
Bradykinesia	0.4–0.9	1.67–3.7
Heel-to-toe difficulties	2.9	0.32
Glabellar tap	4.5	0.13

TESTING—**glabellar tap** (percussion of forehead for ~20 times. Normally blinking stops after 5–10 times. Persistent blinking suggests positive Myerson sign), **bradykinesia maneuvers** (tapping finger, twiddling-like motor, pinching and circling, tapping with heel)

APPROACH—"a combination of tremor, rigidity, bradykinesia, loss of balance, shuffling gait, micrographia, difficulty with turning in bed, opening jars, and rising from a chair should raise suspicion of Parkinson's disease. On examination, the diagnostic value of the classic combination of tremor, rigidity, bradykinesia is limited. Useful signs include the glabellar tap, difficulty walking heel-to-toe and rigidity"

JAMA 2003 289:3
The Rational Clinical Examination. McGraw-Hill, 2009

DISTINGUISHING FEATURES BETWEEN VARIOUS TREMORS

	Parkinson	Essential	Cerebellar
Tremor	Resting	Postural (action)	Intention (action)
Frequency (Hz)	4–6	5–9	3–5
Head direction	Up-down ("yes")	Side-to-side ("no")	None
Legs involved	Yes	Rare	Yes
Effect of alcohol	No change	Improved	No change

CLINICAL FEATURES (CONT'D)

CHARACTERIZING MOVEMENT DISORDERS

- **SPEED**—slow (dystonia, athetosis, dystonic tics), moderate (chorea, tremor, asterixis), quick (myoclonus, myoclonic tics)
- **SUPPRESSIBILITY**—volitional in tics, sensory tricks in dystonia, activity in rest tremor
- **AGGRAVATING FACTORS**—stress, anxiety. Improves with rest and sleep
- **PRECIPITATING FACTORS**—alcohol, caffeine, stress, fatigue, cold, quick movements, prolonged exercises

INVESTIGATIONS

SPECIAL

- **IMAGING**—CT/MR head, particularly if atypical features. Diagnosis of Parkinsons's disease remains clinical

INVESTIGATIONS FOR HYPERKINETIC MOVEMENT DISORDERS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, LDH, CK, INR, PTT, urinalysis
- **IMAGING**—CT head, MRI head

SPECIAL

- **FURTHER NEUROLOGIC WORKUP**—EMG/NCS, muscle/nerve biopsy, lumbar puncture, genetic testing (CAG repeats) and smear for acanthocytes if suspect Huntington's disease
- **INFLAMMATORY WORKUP**—ESR, CRP, ANA, ENA, RF, ANCA, C3, C4, lupus anticoagulant, antiphospholipid antibody, antistreptolysin O
- **MALIGNANCY WORKUP**—quantitative immunoglobulin, serum protein electrophoresis
- **ENDOCRINE WORKUP**—TSH, PTH
- **METABOLIC WORKUP**—vitamin B12, copper, 24 h urinary copper, ceruloplasmin, RBC folate, lactate pyruvate

MANAGEMENT

TREAT UNDERLYING CAUSE

- **SINEMET**—*carbidopa/levodopa* 25/100–25/250 mg PO TID. Risk of dyskinesia. Combined use with entacapone can lead to more sustained levodopa levels. See **NEJM 2008 359:23** for details
- **DOPAMINE AGONISTS**—*bromocriptine* 5–10 mg PO BID, pramipexole, ropinirole, pergolide. Can delay need to initiate levodopa but ineffective in patients unresponsive to levodopa. Risk of impulse control disorders
- **COMT and MAO**-B inhibitors—*entacapone* 200 mg with each dose of levodopa, *rasagiline* 0.5–1 mg PO daily
- **ANTICHOLINERGICS**—*benztropine* 0.5–2 mg PO BID
- **AMANTADINE**—*amantadine* 200–300 mg PO daily
- **APPROACH**—Sinemet should be first-line therapy for most patients because of its effectiveness. COMT/MAO-B inhibitors or dopamine agonists may be used in combination with Sinemet or as first-line agent alone for young patients. Anticholinergics have limited activity but can help with tremor and dyskinesia. Amantadine may be useful for mild disease and dyskinesia
- **DYSKINESIA**—a classic complication of Sinemet. Consider lowering dose of levodopa, changing its timing/frequency, and replacing part of the levodopa dose with a dopamine agonist. Amantadine may be added to counteract dyskinesia

MANAGEMENT (CONT'D)

SYMPTOM MANAGEMENT

- **GENERAL**—education, support, exercise, speech therapy
- **NAUSEA**—domperidone is safe as it does not cross the blood–brain barrier. Avoid antidopaminergic medications such as metoclopramide and phenothiazines (prochlorperazine, chlorpromazine)
- **PSYCHOSIS AND HALLUCINATIONS**—consider stopping anti-Parkinsonian drugs in sequence. May need to start atypical neuroleptic antipsychotics such as quetiapine or clozapine. Avoid older neuroleptic antipsychotics such as haloperidol
- **DEPRESSION**—antidepressants such as TCAs and SSRIs may be used with caution

SPECIFIC ENTITIES

GAIT ASSESSMENT

- **GENERAL INSPECTION**—inspect pelvis, knees, ankles, and feet for asymmetry, deformity. Ask the patient to walk normally, then heel-to-toe, walk on heels, walk on toes, and squat (testing strength, coordination)
- **FOOT MOVEMENTS**—heel strike, foot flat (mid-stance), heel off (lift off), toes off (swing)
- **GAIT MOVEMENTS**—comment on pace length, width, coordination, and stability (see table below for specific pathologies)
- **NEUROLOGICAL EXAMINATION**—lower limb motor and sensory examination. Also include Romberg test

Type	Pathology
Spastic gait	Upper motor neuron lesion (stroke)
Scissor gait	Bilateral upper motor neuron disease
Apraxic/magnetic gait	Frontal lobe (NPH, stroke)
Shuffling gait	Extrapyramidal lesion (Parkinson's)
Broad based gait	Cerebellar—vermis
Ataxic gait	Cerebellar—anterior (alcohol)
Unsteady, sensory ataxia gait	Posterior column (Tabes dorsalis, B12 deficiency, Friedreich's ataxia)
Trendelenburg gait (waddling)	Hip adductor muscle weakness (gluteus medius)
Steppage gait	Foot drop (peroneal nerve palsy)

Related Topics
Dementia (p. 429)
Orthostatic Hypotension (p. 354)

Radiculopathy

NEJM 2005 353:4

PATHOPHYSIOLOGY

FORAMINAL ENCROACHMENT OF THE SPINAL NERVE—usually due to a combination of decreased disc height and degenerative changes of the uncovertebral joints anteriorly and zygapophyseal joints posteriorly

COMMONLY AFFECTED NERVE ROOTS

- **CERVICAL REGION**—C7 (70%) and C6 (20%) are the most commonly affected nerve roots
- **LUMBOSACRAL REGION**—L5 and S1 (>90% combined) are the most commonly affected nerve roots

Related Topics
Back Pain (p. 322)
Peripheral Neuropathy (p. 371)
Spinal Cord Compression (p. 253)

CLINICAL FEATURES

HISTORY—characterize neck or back pain. Paresthesia, radiation of pain, and weakness over specific nerve root distribution, any associated neurological symptoms. Ask about risk factors for radiculopathy (e.g. spinal injury or trauma) as well as peripheral neuropathy (e.g. diabetes mellitus, nerve entrapment, repetitive strain, prolonged kneeling, or recent musculoskeletal trauma). Ask about reproduction of symptoms with axial compression, Valsalva maneuver, or positional change. Ask about red flags (fever, chills, unexplained weight loss, unremitting night pain, previous cancer, immunosuppression, and IDU) which may suggest tumor or infections

SPURLING'S SIGN—reproduction of symptoms with extension and lateral rotation of neck toward

CLINICAL FEATURES (CONT'D)

affected side followed by compressive force to the top of the head suggests cervical radiculopathy (LR+ 3.6). Caution as there is risk of spinal injury in patients with rheumatoid arthritis, cervical malformations, or metastatic disease

INVESTIGATIONS

IMAGING—spine X-ray (low sens), CT spine, MR spine (especially if suspect radiculopathy/myelopathy, red flags, progressive neurologic deficits, no improvement for 4–6 weeks), myelography (rarely used now)

EMG AND NERVE CONDUCTION STUDY

TREATMENT OF CERVICAL RADICULOPATHY

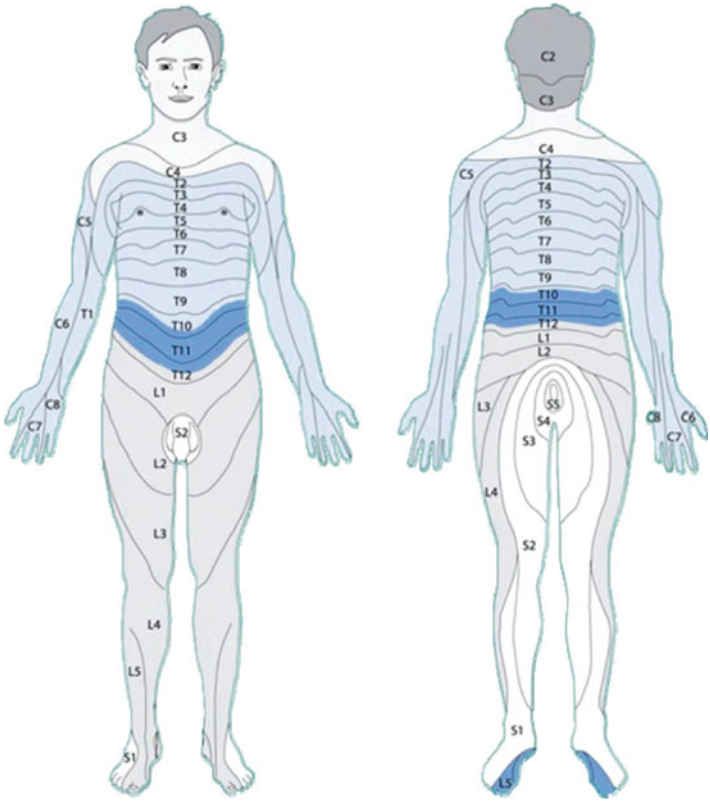
NON-SURGICAL—acetaminophen, NSAIDs, opioids, corticosteroid injections, cervical traction, exercise

SURGICAL—indicated if myelopathy or a combination of definite cervical root compression by CT/MRI, radiculopathy symptoms/signs, and persistent pain despite non-surgical treatment of 6–12 weeks or progressive motor weakness

SPECIFIC ENTITIES

CERVICAL MYELOPATHY—diffuse hand numbness and clumsiness (often attributed to peripheral neuropathy), imbalance, sphincter disturbances (late finding, urinary urgency/frequency initially, then retention or incontinence). Physical findings include hypertonia, hyperreflexia/clonus, positive Babinski, Hoffmann's (flexion and adduction of the thumb when the examiner flexes the terminal phalanx of the long finger), and Lhermitte's sign

DERMATOMES



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MYOTOMES

Root	Muscles
C3,4,5	Diaphragm
C5	Deltoid (**shoulder abduction**)
C6	Biceps and brachioradialis (**elbow flexion**), radial wrist extensors (wrist extension)
C7	Triceps (**elbow extension**), ulnar wrist extensors (wrist extension), wrist flexors, finger extensors
C8	Intrinsic muscles of hand (finger flexion/extension)
T1	Intrinsic muscles of hand (finger abduction/adduction)
T2–12	Chest wall and abdominal muscles
L2	Iliopsoas (**hip flexion**)
L3	Quadriceps (**knee extension**), adductor longus (**hip adduction**)
L4	Quadriceps (**knee extension**), tibialis anterior (**dorsiflexion and inversion**)

MYOTOMES (CONT'D)

Root	Muscles
L5	Extensor hallucis longus (**big toe extension**), tibialis posterior (planterflexion and eversion), gluteus medius (hip abduction)
S1	Gluteus maximus (**hip extension**), gastrocnemius, soleus, peroneus longus (plantar flexors, eversion)
S2,3,4	Bowel, bladder, sexual organs, anal other pelvic muscles

Note: may have some overlap between myotomes and peripheral nerve roots

BRACHIAL PLEXUS

Nerve	Root/origin	Muscle function
Dorsal scapular	C4**5** Root level	Rhomboids (retracts scapula)
Long thoracic	C5**6**7 Root level	Serratus anterior (scapula abduction)
Suprascapular	C**5**6 Upper trunk	Supraspinatus (arm abduction) Infraspinatus (arm external rotation)
Lateral anterior thoracic	C6**7** Upper, middle trunk	Pectoralis major (arm adduction, internal rotation)
Medial anterior thoracic	C**8** Lower trunk	Pectoralis major (arm adduction, int. rotation) Pectoralis minor (protracts scapula)
Subscapular	C**5**6 Posterior cord	Subscapularis (arm adduction) Teres major (arm extension, ext. rotation)
Thoracodorsal	C**7**8 Posterior cord	Latissimus dorsi (arm extension, adduction, internal rotation)
Axillary	C**5** Posterior cord	Deltoid (arm abduction) Teres minor (arm external rotation)
Musculo-cutaneous	C**5**6 Lateral cord	Biceps (forearm flexion) Brachioradialis (supination)
Median	C**567T1** Anterior cord	See tables below
Radial	C**678** Posterior cord	See tables below
Ulnar	C**8T1** Lateral cord	See tables below

MUSCLE–NERVE FUNCTION CORRELATION

Muscle	Innervation	Function
Tibialis anterior	Deep peroneal n. (L4**L5**S1)	Inversion, **dorsiflexion**
Tibialis posterior	Tibial n. (**L4**L5)	**Inversion**, planterflexion
Peroneus longus	Superficial peroneal n.(L5**S1**)	**Eversion**, planterflexion
Peroneus brevis	Superficial peroneal n.(L5**S1**)	**Eversion**, planterflexion

DIFFERENTIATING BETWEEN NERVE ROOT AND PERIPHERAL NERVE LESIONS

C6 VS. MEDIAN NERVE LESION

	C6	Median nerve (C6-T1)
Sensory	Palmer and dorsal surfaces of 1st-2nd fingers (including **anatomical snuff box**), lateral surface of arm/forearm	Palmer surface of **1st**, **2nd**, **and 3rd fingers and lateral portion of 4th finger**

DIFFERENTIATING BETWEEN NERVE ROOT AND PERIPHERAL NERVE LESIONS (CONT'D)

	C6	Median nerve (C6-T1)
Motor	**Biceps** (musculocutaneous nerve), **brachioradialis** (musculocutaneous nerve), **supinatator** (radial nerve)	★**LOAF**★ **L**ateral lumbricals (1st and 2nd), **O**pponens pollicis (opposition), **A**bductor pollicis brevis (abduction of thumb), **F**lexor pollicis brevis (flexion of thumb/fingers)
Reflex	**Biceps**, **brachioradialis**	None
Other	Reproduction of symptoms with axial compression or positional change	Inspect for Benediction sign (index ± middle finger held in extension; associated with median nerve injury at or above the elbow), percuss for Tinel sign (over carpal tunnel), palpate for Durkan's test (direct compression over carpal tunnel), flex at wrist for Phalen sign, and perform Ochsner's clasping test (index finger fails to flex)

C7 VS. RADIAL NERVE LESION

	C7	Radial nerve (C5–T1)
Sensory	**Palmer surface of 3rd finger**	Dorsal surface of 1st, 2nd, and 3rd fingers and lateral portion of 4th finger (including **anatomical snuff box**)
Motor	**Pronator teres** (median nerve), adduction of shoulder by **latissimus dorsi** (thoracodosal nerve) and **pectoralis major** (lateral and medial pectoral nerves)	★**BEST**★ **B**rachioradialis (radial nerve), **E**xtensor pollicis longus (posterior interosseous nerve), **E**xtensor indicis (posterior interosseous nerve), **S**upinator (posterior interosseous nerve), **T**riceps (radial nerve)
Reflex	Note: triceps reflex does not reliably differentiate between C7 vs. radial nerve lesion	**Brachioradialis**
Other	Reproduction of symptoms with axial compression or positional change	Inspect for wrist drop and examine mid-humerus for trauma or injury

C8/VS. ULNAR NERVE LESION

	C8	Ulnar nerve (C8T1)
Sensory	**Medial aspect of forearm**, palmar and dorsal surface of 4th and 5th fingers	Note: sensation to palmar and dorsal surfaces of 4th and 5th fingers does not reliably differentiate between C8 vs. ulnar nerve lesion (affected in both)
Motor	**Extensor indicis** (posterior interosseous nerve), **extensor pollicis longus** (posterior interosseous nerve), **flexor pollicis longus** (anterior interosseous nerve), **LOAF muscles** (median nerve)	**Adductor pollicis**, first dorsal interosseous muscle Note: motor activity of lumbricals (3rd, 4th), interossei 5th finger opposition, abduction and flexion, as well as thumb adduction do not reliably differentiate between C8 vs. ulnar nerve lesion (affected in both)
Reflex	**Flexion of fingers of lateral two lumbricals**	None

DIFFERENTIATING BETWEEN NERVE ROOT AND PERIPHERAL NERVE LESIONS (CONT'D)

	C8	Ulnar nerve (C8T1)
Other	Reproduction of symptoms with axial compression or positional change	Inspect for claw hand, percuss for Tinel sign (in groove between medial epicondyle and the olecranon), and perform Froment's test (patient pinches sheet of paper between thumb and index finger; pulling paper away reveals **weakness of adductor pollicis** and compensatory flexion of IP joint of the thumb)

L4 VS. FEMORAL NERVE LESION

	L4	Femoral nerve (L234)
Sensory	Note: sensation from lateral leg to medial malleolus does not reliably differentiate between L4 vs. femoral nerve lesion (affected in both)	**Medial leg**
Motor	**Hip adductors** (obturator nerve), ankle dorsiflexion with **tibialis anterior** (deep peroneal nerve)	Note: hip flexion and knee extension does not reliably differentiate between L4 vs. femoral nerve lesion (affected in both)
Reflex	**Hip adductor jerk**	Note: knee jerk reflex does not reliably differentiate between L4 vs. femoral nerve lesion (affected in both)
Other	Straight leg raise and femoral nerve stretch test (for nerve root impingement)	Inspect for hematoma (for nerve entrapment)

L5 VS. PERONEAL NERVE LESION

	L5	Common peroneal n. (L45S1)
Sensory	Note: some sources claim that L5 uniquely provides sensation to lateral aspect of foot and little toe, but this is probably supplied by the sural nerve/lateral dorsal cutaneous nerve (S1). Does not reliably differentiate between L5 vs. common peroneal nerve lesion	Note: sensation to lateral leg and dorsal foot (including web space between big toe and 2nd toe) does not reliably differentiate between L5 vs. common peroneal nerve lesion (affected in both)
Motor	Ankle inversion with **posterior tibialis** (tibial nerve), hip abduction from **gluteus medius and minimus** (superior gluteal nerve), hip extension with **gluteus maximus** (inferior gluteal nerve), and knee flexion with **hamstrings** (sciatic nerve)	Note: dorsiflexion (deep peroneal nerve), eversion (superficial peroneal nerve), and great toe dorsiflexion (deep peroneal nerve) do not reliably differentiate between L5 vs. common peroneal nerve lesion (affected in both)
Other	Straight leg raise	Tinnel sign (percussion over fibular head)

L5 VS. SCIATIC NERVE LESION

	L5	Sciatic nerve (L4–S3)
Sensory	Note: sensation to lateral leg and dorsal foot does not reliably differentiate between L5 vs. sciatic nerve lesion	**Lateral aspect of foot** (**little toe**)

DIFFERENTIATING BETWEEN NERVE ROOT AND PERIPHERAL NERVE LESIONS (CONT'D)

	L5	Sciatic nerve (L4–S3)
Motor	Hip abduction from **gluteus medius and minimus** (superior gluteal nerve), hip extension with **gluteus maximus** (inferior gluteal nerve)	Ankle plantarflexion with **gastrocnemius and soleus** (tibial nerve) Note: ankle eversion and knee flesion do not reliably differentiate between L5 vs. sciatic nerve lesion (affected in both)
Reflex	None	Ankle jerk
Other	Straight leg raise	Palpation of sciatic nerve

For the nerve root/peripheral nerve lesions tables above,
BOLD = highlights important differences between nerve root and peripheral nerve lesions
REFLEXES—complete peripheral nerve lesions will lead to complete areflexia, while complete nerve root lesions will only lead to partial reduction of reflexes

SPECIFIC CONSIDERATIONS

DISTINGUISHING FEATURES BETWEEN MEDIAN NERVE LESION, ULNAR NERVE LESION, AND T1 RADICULOPATHY—these lesions can be differentiated by testing two muscles: abductor pollicis brevis is supplied by the median nerve (i.e. supinate hand, point thumb toward ceiling, test power by pushing thumb down), while first dorsal interosseous is supplied by the ulnar nerve (i.e. test power of index finger abduction)

Lesion	Abductor pollicis brevis	1st dorsal interosseous
T1 radiculopathy	Weak	Weak
Median nerve	Weak	Spared
Ulnar nerve	Spared	Weak

NOTE: may also test little finger abduction (abductor minimi digiti) to assess ulnar nerve integrity

Peripheral Neuropathy

DIFFERENTIAL DIAGNOSIS

MONONEUROPATHY—compression, infiltration, mononeuritis
MONONEURITIS MULTIPLEX—vasculitis, diabetes
POLYNEUROPATHY

- **AXONAL INJURY**
  - **NEOPLASTIC**—carcinoma, lymphoma, MGUS-IgA, IgG, IgM
  - **INFECTIOUS**—sepsis, HIV, Lyme
  - **METABOLIC**—diabetes, uremia
  - **VITAMIN DEFICIENCY**—malabsorption
  - **DRUGS**—cisplatin, taxanes, vincristine, isoniazid, nucleoside analogue
- **DEMYELINATING**—Guillain–Barre, neoplastic (carcinoma, lymphoma, MGUS-IgM), drugs (taxanes), chronic inflammatory demyelinating polyradiculoneuropathy

CLINICAL FEATURES

HISTORY—sensory loss, pain, dysesthesias, burning, gait abnormalities, weakness, past medical history (diabetes, medications, malignancy, infections), family history. Assess time course, distribution (length-dependent, 'stocking and glove', migration and progression)
PHYSICAL—muscle wasting, muscle strength, sensation to pin prick, light touch, vibration, temperature, proprioception, reflexes
DIFFERENTIATING SITE OF MEDIAN NERVE INJURY—if lesion at carpal tunnel, LOAF muscles affected. If lesion at or above the elbow, there may be lateral forearm wasting and the index finger held in extension (Benediction sign)
DIFFERENTIATING SITE OF ULNAR NERVE INJURY—low lesion (below the wrist) characterized by marked hand clawing (because of

CLINICAL FEATURES (CONT'D)

unopposed flexor digitorum profundus flexion of DIPs). High lesions have subtle clawing, termed ulnar paradox

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, ESR, serum protein electrophoresis, vitamin B12, ANA, TSH, urinalysis

SPECIAL

- **EMG AND NERVE CONDUCTION STUDY**
- **NERVE/MUSCLE BIOPSY**
- **LUMBAR PUNCTURE**
- **INFECTIOUS WORKUP**—Lyme serology, HIV, RPR, HBV/HCV serology

MANAGEMENT

TREAT UNDERLYING CAUSE—**diabetic** (glucose control), **lymphoma**/**myeloma** (chemotherapy)

SYMPTOM MANAGEMENT—**tricyclic antidepressants** (*desipramine* 10–50 mg qhs), ***gabapentin*** (300 mg PO daily × 1 day, then 300 mg PO BID × 1 day, then 300 mg PO TID, max 1800 mg/day), **pregabalin**, **anticonvulsants** (topiramate, carbamazepine)

SPECIFIC ENTITIES

CARPEL TUNNEL SYNDROME

- **PATHOPHYSIOLOGY**—median nerve entrapment syndrome
- **ASSOCIATIONS**—repetitive use, acromegaly, amyloidosis, hypothyroidism, rheumatoid arthritis, diabetes mellitus, pregnancy, and mucopolysaccharidosis. Bilateral disease or early involvement of non-dominant hand suggests a systemic condition
- **DIAGNOSIS**—nerve conduction studies (sens 49–84%, spc 95–99%) should be done if inadequate response to conservative therapy (changes in the workplace, night-time neutral splints), thenar atrophy, or if the diagnosis is unclear
- **TREATMENTS**—activity modifications, wrist splinting, NSAIDs, corticosteroid injections (success 49–81%, recurrence 50–86%), carpel tunnel release (success 75–99%)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE CARPEL TUNNEL SYNDROME?

KATZ HAND DIAGRAM—**classic** (tingling of at least two of digits 1–3. The classic pattern permits symptoms in the 4th and 5th digits, wrist pain, and radiation of pain to wrist, but not symptoms on the palm/dorsum of the hand), **probable** (same symptom pattern as classic, except palmer symptoms are allowed unless confined solely to the ulnar aspect), **possible**, **unlikely**

	LR+	LR–
History		
Classic/probable Katz diagram	2.4	0.5
Age >40	1.3	0.5
Nocturnal paresthesia	1.2	0.7
Bilateral symptoms	1.4	0.7
Physical		
Hypalgesia (↓ pain sensation) in the median nerve territory	3.1	0.7
Abnormal vibration	1.6	0.8
Weak thumb abduction strength	1.8	0.5
Thenar atrophy	1.6	1.0
Square wrist sign	2.7	0.5
Closed fist sign	7.3	0.4
Flick sign	1.4	0.1
Tinel's sign	1.5	0.8
Phalen's sign	1.3	0.7

SPECIFIC ENTITIES (CONT'D)

APPROACH—"Katz hand symptom diagrams, hypalgesia, and thumb abduction strength testing are helpful in establishing diagnosis of carpel tunnel syndrome"

JAMA 2000 283:23

UPDATE—Flick sign, Tinel's sign, and Phalen's sign are not helpful in making the diagnosis of CTS. In addition, clinical provocation maneuvers do not significantly alter the likelihood of CTS

The Rational Clinical Examination. McGraw-Hill, 2009

SPECIFIC ENTITIES (CONT'D)

AUTONOMIC NEUROPATHY

- **CAUSES**—autonomic failure may be secondary to peripheral neuropathy associated with diabetes, cancer (paraneoplastic), amyloidosis, cachexia, HIV, Guillain–Barre syndrome, Lambert–Eaton syndrome, other inflammatory/infectious conditions, or due to primary disorders such as Parkinson's disease, Shy–Drager syndrome (multiple system atrophy with autonomic failure), Lewy body dementia, and multiple sclerosis

	Sympathetic dysfunction	Parasympathetic dysfunction
Vitals	Orthostatic hypotension	Tachycardia
Skin	Warm and moist	Cool and dry
H&N	Horner's	Dry eyes + mouth Dilated pupil
Heart	No respiratory variation	
GI/GU		Constipation Distended bladder Impotence
MSK, gait	Postural instability	

Related Topics
Diabetic neuropathy (p. 381)
Radiculopathy (p. 366)

SPECIFIC ENTITIES

GUILLAIN–BARRE SYNDROME (GBS)

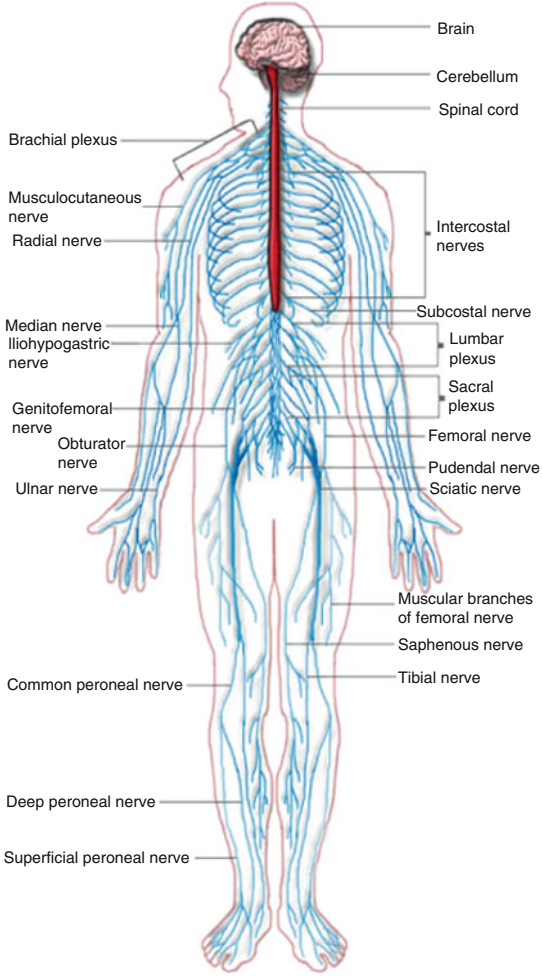
- **PATHOPHYSIOLOGY**—precipitants (*Campylobacter jejuni* [ask about bloody diarrhea], CMV infection, upper respiratory tract infections, possibly flu shots) → acute inflammatory demyelinating polyradiculoneuropathy 2–4 weeks later → reach nadir of symptoms 2–4 weeks (25% require mechanical ventilation) → recovery weeks to months

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—fine paresthesias in toes and fingertips → weakness in lower/upper extremities (often ascending) → potential autonomic dysfunction (50%), cranial nerves, respiratory muscle involvement. **Areflexia** is a key feature (but may be preserved early-on) but presence of hyper-reflexia strongly suggests alternative diagnosis (e.g. transverse myelitis). Low/mid-back pain common
- **SUBTYPES**—four subtypes include demyelinating (acute inflammatory demyelinating polyradiculoneuropathy), axonal motor (acute motor axonal neuropathy), axonal motor and sensory (acute motor and sensory axonal neuropathy), and Miller–Fischer syndrome (ophthalmoplegia, ataxia, areflexia)
- **DIAGNOSIS**—EMG (demyelinating neuropathy), lumbar puncture (albuminocytologic dissociation = normal CSF WBC but ↑ CSF protein), PFT (↓ FVC, MIP, MEP)
- **TREATMENTS**—*IVIG* 0.5–1 g/kg IV daily, plasma exchange. ICU admission with respiratory support if FVC <20 mL/kg, maximum inspiratory pressure <30 cmH_2O, maximum expiratory pressure <40 cmH_2O, rapid progression <7 days, cranial or autonomic involvement

MONONEURITIS MULTIPLEX—simultaneous/sequential involvement of multiple named nerves (e.g. median, ulnar, radial, peroneal nerves). Multiple nerve infarcts due to a systemic vasculitis

PERIPHERAL NERVES



Reprinted from http://en.wikipedia.org/wiki/File:Nervous_system_diagram.png

PERIPHERAL NERVES (CONT'D)

MONONEUROPATHIES

Nerve (origin)	Pathophysiology	Signs and symptoms	Comments
Axillary nerve (C5–6)	Lesion usually near shoulder joint	Motor: weakness of shoulder abduction, shoulder atrophy	
	Affects deltoid and teres minor	Sensory: deficit similar to C5 lesion	
Subscapular nerve (C5–6)	Lesion usually at suprascapular notch of scapula	Motor: weakness of external rotation of arm	
	Affects supraspinatus and infraspinatus	Sensory: intact	
Long thoracic nerve (C5–7)	Affects serratus anterior	Motor: winging of the scapula Sensory: intact	
Radial nerve (C5–T1)	Lesion usually at spiral groove of humerus	Motor: wrist drop, weakness of finger and thumb extensors	Saturday night palsy (acute compression) is frequent cause
	Affects brachioradialis, triceps, wrist, finger and thumb extensors	Sensory: changes in dorsal surface of 1st-lateral 4th fingers, dorsal surface of arm/forearm	Cheiralgia paresthetica (entrapment of superficial branch of radial nerve to dorsum of hand)
Posterior interosseous branch of radial nerve (C7–8)	Lesion usually at the Arcade of Foshse	Motor: finger drop, wrist relatively spared	
	Affects finger and thumb extensors	Sensory: intact	
Ulnar nerve (C8–T1)	Lesion usually at cubital tunnel or ulnar groove at the elbow	Motor: weakness of finger adduction, abduction and thumb adduction (Froment's sign), claw-hand and interosseous atrophy	
	Affects ulnar flexor of the wrist, long flexors of 4th-5th digits and intrinsic hand muscles	Sensory: changes in both dorsal and palmer surfaces of 4th and 5th fingers. May have pain over median proximal forearm (cubital tunnel). Tests: Tinel sign positive	
Ulnar nerve (C8–T1)	More distal lesion usually at medial base of palm	Motor: weakness of finger adduction and abduction. Interosseous atrophy	Cyclist's palsy
	Affects intrinsic hand muscles only	Sensory: changes in palmer surface of 4th and 5th fingers only Tests: Tinel sign negative	
Median nerve (C6–T1)	Lesion at carpal tunnel	Motor: weakness, pain, numbness and tingling over thumb, 2nd and 3rd fingers	Carpel tunnel syndrome

PERIPHERAL NERVES (CONT'D)

Nerve (origin)	Pathophysiology	Signs and symptoms	Comments
	Affects abductor pollicis brevis, proximal muscles include forearm pronator, long finger, and thumb flexors	Sensory: changes in palmer surface of 1st-lateral 4th fingers	
		Tests: square wrist sign, closed fist sign, Flick sign, Tinel sign and Phalen sign	
Anterior interosseous branch of median nerve (C7–T1)	Lesion usually just below the elbow	Motor: weakness of pinch, pain in volar forearm	
	Affects long flexors of thumb and index and middle fingers	Sensory: intact	
Femoral nerve (L2–4)	Lesion usually proximal to inguinal ligament	Motor: buckling of knee, absent knee jerk, weak anterior thigh muscles with atrophy.	Post-femoral catheterization or pelvic surgery with retroperitoneal hematoma, diabetes mellitus
	Affects iliopsoas (hip flexor) and quadriceps femoris (knee extensor)	Sensory: changes in lateral leg to medial malleolus	
Lateral femoral cutaneous branch of femoral nerve (L2–3)	Lesion usually at inguinal ligament	Motor: intact	Meralgia paresthetica (entrapment of lateral cutaneous femoral nerve to anterolateral aspect of thigh)
		Sensory: dysesthetic hyperpathia of lateral thigh (burning)	
Obturator nerve (L3–4)	Lesion usually at pubis or intrapelvic	Motor: weakness of hip adduction	
	Affects thigh adductors	Sensory: deficit of medial thigh	
Sciatic nerve (L4–S3)	Lesion usually near sciatic notch	Motor: severe lower leg and hamstring weakness, flail foot, difficulty walking	Overdose victims
	Affects hamstring muscles, hip abductor and all muscles below the knee	Sensory: changes in lower leg and foot	
Tibial nerve (L5–S2)	Lesion usually at tarsal tunnel or near medial malleolus	Motor: weak toe flexors	Tarsal tunnel syndrome
	Affects calf muscles (proximally), toe flexor, and other intrinsic foot muscles	Sensory: pain and numbness of sole	
Peroneal nerve (L4–S1)	Lesion usually at neck of fibula	Motor: weakness of foot eversion and foot drop	Cross-leg palsy
	Affects dorsiflexors of toes and foot and evertors of foot	Sensory: deficit similar to L5 lesion	

Muscle Weakness

DIFFERENTIAL DIAGNOSIS

INFLAMMATORY MYOPATHY—polymyositis, dermatomyositis, inclusion body myositis, juvenile dermatomyositis, vasculitis, overlap syndromes (SLE, scleroderma, rheumatoid arthritis, Sjogren's)

INFECTIOUS MYOPATHY

- **BACTERIAL**—pyomyositis, Lyme myositis
- **VIRAL**—influenza, parainfluenza, Coxsackie, HIV, CMV, echovirus, adenovirus, EBV
- **FUNGAL**
- **PARASITIC**—trichinosis, toxoplasmosis

DRUG/TOXIC MYOPATHY—steroid, alcohol, cocaine, heroin, colchicine, antimalarial, statins, fibrates, penicillamine, zidovudine, gemcitabine

ENDOCRINE MYOPATHY—hypothyroidism, hyperthyroidism, Cushing's, diabetes, acromegaly

METABOLIC MYOPATHY—hypokalemia, hypocalcemia, hypophosphatemia, hyponatremia, hypernatremia, disorders of carbohydrate/lipid/purine metabolism

NEOPLASTIC MYOPATHY—paraneoplastic

RHABDOMYOLYSIS

- **DRUGS**—alcohol, cocaine, statins, neuroleptic malignant syndrome, malignant hyperthermia
- **HYPERACTIVITY**—seizures, exertion
- **TRAUMA/OPERATION**
- **IMMOBILITY**

NEUROLOGIC

- **MOTOR CORTEX**—stroke, multiple sclerosis, brain tumor, abscess
- **CORTICOSPINAL TRACT/ANTERIOR HORN CELLS**—spinal cord injury, vitamin B12 deficiency, ALS, polio, lead
- **SPINAL NERVE ROOTS/PERIPHERAL NERVES**—Guillain–Barre, myeloma, amyloidosis, diabetes
- **NEUROMUSCULAR JUNCTION**—myasthenia gravis, botulism, Eaton–Lambert, organophosphate poisoning
- **MUSCLES**—myopathies (see above)

Related Topics
Critical Illness Weakness (p. 99)
Dermatomyositis (p. 316)
Eaton-Lambert Syndrome (p. 361)
Myasthenia Gravis (p. 360)

CLINICAL FEATURES

APPROACH TO CLINICAL DIAGNOSIS

1. **FUNCTIONAL VS. TRUE MUSCLE WEAKNESS?**
   - If functional, consider cardiopulmonary disease, arthritis, anemia, cachexia from malignancy or chronic disease, depression, deconditioning, fibromyalgia
   - If true muscle weakness, proceed to 2
2. **GENERALIZED VS. LOCALIZED MUSCLE WEAKNESS?**
   - If generalized, consider myasthenia gravis, long-standing periodic paralysis, advanced disuse atrophy from prolonged bed rest, or advanced muscle wasting from malignancy
   - If localized, proceed to 3
3. **ASYMMETRIC VS. SYMMETRIC MUSCLE WEAKNESS?**
   - If asymmetric, consider disease of central or peripheral nervous system (stroke, spinal cord injury, demyelinating disorders, compression neuropathy, mononeuropathy/neuritis), disuse atrophy, myasthenia gravis
   - If symmetric, proceed to 4
4. **DISTAL VS. PROXIMAL MUSCLE WEAKNESS?**
   - If distal, consider peripheral neuropathy, myasthenia gravis, motor neuron disease
   - If proximal, consider myopathies (see differential diagnosis), myasthenia gravis, muscular dystrophy

MRC MUSCLE STRENGTH GRADING

0 = NO CONTRACTION
1 = FLICKER
2 = POSSIBLE ONLY WITH GRAVITY ELIMINATED
3 = AGAINST GRAVITY ONLY
4 = POWER DECREASED BUT MUSCLE CONTRACTION POSSIBLE AGAINST RESISTANCE
5 = NORMAL POWER RESISTANCE

MUSCLE STRENGTH—preserved in patients with cachexia despite advanced generalized muscle atrophy. In contrast, patients with true muscle weakness due to myopathy generally have normal muscle bulk at time of presentation

MUSCLE TENDERNESS—usually not associated with one of the causes of true muscle weakness, except for infectious myopathies, certain drug-induced myopathies, rhabdomyolysis, thyroid myopathy, and inherited metabolic myopathies

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, Ca, Mg, PO_4, CK, TSH, LDH, AST, ALT, ANA, ANCA, HBV/HBC serology, cryoglobulin, RF

SPECIAL

- **EMG AND NERVE CONDUCTION STUDY**
- **MUSCLE BIOPSY**—select mildly-affected muscle, not previously studied with EMG
- **POLYMYOSITIS/DERMATOMYOSITIS WORKUP**—anti-Jo 1 and 2, anti-SRP (signal recognition particle), anti-Mi2
- **MRI**—can be used to identify muscle for biopsy

MANAGEMENT

REHABILITATION
TREAT UNDERLYING CAUSE

SPECIFIC ENTITIES

CRITICAL ILLNESS NEUROMUSCULAR DISORDERS

- **CRITICAL ILLNESS POLYNEUROPATHY**—muscle weakness and atrophy, ↓ deep tendon reflexes, ↓ peripheral sensation to light touch and pin prick. Associated with sepsis, systemic inflammation

SPECIFIC ENTITIES (CONT'D)

- **DELAYED REVERSAL OF NEUROMUSCULAR BLOCKADE**—non-depolarizing neuromuscular blocking agents (pancuronium, vecuronium) in susceptible patients
- **CRITICAL MYOPATHY**—muscle weakness and atrophy. Muscle damage second degree to sepsis and multi-system organ failure. Sensation invariably spared. EMG and muscle biopsy can be diagnostic
- **MYOPATHY ASSOCIATED WITH COMBINED USE OF STEROID AND NEUROMUSCULAR BLOCKING AGENT**—muscle weakness and atrophy, ↑ deep tendon reflexes

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

- **PATHOPHYSIOLOGY**—combined upper and lower motor neuronal degeneration → spread to involve multiple myotomes in multiple regions (bulbar, cervical, and lumbosacral). No sensory deficit. Preserved cognition
- **CLINICAL FEATURES**—mixed upper motor neuron signs (hyperactive reflexes, extensor plantar responses) and lower motor neuron signs (muscle weakness, atrophy, and fasciculations) in multiple regions
- **DIAGNOSIS**—EMG/NCS
- **TREATMENTS**—antiglutamate agent (riluzole)

DROP HEAD SYNDROME—persistent head flexion. May be due to myasthenia gravis, polymyositis, or amyotrophic dystonia

Approach to Neuroimaging

MODALITIES

CT HEAD (unenhanced)—particularly useful for **acute hemorrhage** (subarachnoid, subdural, intracerebral), **skull fractures/trauma**, **meningiomas**, **and subacute and chronic strokes**. Also used as initial workup of acute TIA or stroke and other brain tumors although not as sensitive as MRI. Advantages include easy accessibility. Disadvantages include insensitivitiy in detecting subtle structural pathology and changes in the posterior fossa

MRI HEAD—particularly useful for evaluation of **stroke** (acute, subacute, chronic), **hemorrhage** (subacute and chronic), **white matter lesions** (multiple sclerosis), and lesions of the **posterior fossa**, **brainstem**, and **spinal cord**. Also useful for most tumors, epilepsy, demyelinating diseases, inflammatory and infectious conditions

MODALITIES (CONT'D)

(e.g. HSV encephalitis), degenerative diseases, and congenital abnormalities. Main disadvantage is difficulty scanning patients with claustrophia

MRI WITH GADOLINIUM—certain lesions and pathological findings have characteristic enhancement patterns. Gadolinium enhancement may be seen in some infectious, inflammatory, and neoplastic conditions (from breakdown of blood-brain barrier)

CT/MR ANGIOGRAPHY—used for evaluation of occlusive cerebrovascular disease, dissection, and in the detection of intracerebral aneurysms as small as 5 mm in diameter. However, conventional cerebral angiogram remains the gold standard

CT/MR VENOGRAPHY—extremely sensitive and specific in the diagnosis of venous sinus thrombosis

APPROACH TO CT HEAD

BRAIN PARENCHYMA

- **ANY SUSPICIOUS, ASYMMETRIC LESIONS**—hypodensity within the parenchyma suggests infarction or fluid. Hyperdensity represents either hematoma (hemorrhage) or calcification. A hematoma will produce mass effect upon adjacent structures. Calcification will usually be punctate and have no mass effect
- **GRAY–WHITE DIFFERENTIATION**—the junction of gray matter and white matter adjacent to the cortex and the basal ganglia should be well defined. Poor delineation should raise suspicion of cerebral edema if the finding is global or acute infarction if the finding is localized
- **MIDLINE SHIFT**—measured by drawing a line from the anterior falx to the posterior falx, then comparing this line with the septum pellucidum

VENTRICLES AND SUBARACHNOID SPACES (sulci and cisterns)—difficulty with visualization of the basal cisterns may indicate increased intracranial pressure and possibly brain herniation. Hyperdensity (white) within the subarachnoid spaces and the dependent portions of the ventricles suggests subarachnoid hemorrhage

DURA AND SUBDURAL SPACE—check for subdural hemorrhage in subdural window (crescent like), especially along the edges of the intracranial cavity

BONE AND AIR SPACES—check for fractures in bone window and fluid in sinuses

SKIN AND SUBCUTANEOUS TISSUES—check for swelling of extracranial soft tissues in subdural window

HEAD CT FINDINGS IN THE ELDERLY

SMALL VESSEL DISEASE—diffuse brain atrophy, hypodense periventricular white matter due to gliosis, and lacunar infarcts within the basal ganglia

LARGER VENTRICLES AND SUBARACHNOID SPACES—due to brain atrophy

FOCAL CALCIFICATION—common within the basal ganglia in the elderly and should not be confused with hemorrhage

HEAD CT FINDINGS IN STROKE

LOCALIZATION—the presenting symptoms can help focus evaluation. The majority of infarcts involve the MCA territory or subcortical region. Early signs of infarction include the following:

- **HYPERDENSE MCA**—the suspected MCA must be significantly denser than the contralateral MCA or basilar artery
- **EDEMA OF THE BASAL GANGLIA AND/OR INSULAR CORTEX**—involved lentiform nucleus will appear hypodense with indistinct lateral border. The insular cortex will appear swollen compared to the contralateral side
- **SULCAL EFFACEMENT**—the sulci along the cerebral convexity on the involved side will appear smaller than the other side

EVOLUTION—hypodense lesions may not appear until after 24 h. MRI is superior to CT for identifying acute stroke. Lesions may become more hypodense over time. Old infarcts are very black

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ENDOCRINOLOGY

Sonia Butalia

Diabetes Mellitus — Canadian Diabetes Association Guidelines 2013

CLASSIFICATION

TYPE 1 DIABETES—autoimmune destruction of β cells, prone to DKA

TYPE 2 DIABETES—insulin resistance and a relative or absolute insulin deficiency

GESTATIONAL DIABETES—glucose intolerance diagnosed during pregnancy

OTHER SPECIFIC TYPES

- **GENETIC DEFECTS OF β CELL FUNCTION**—maturity onset diabetes of the young (MODY)
- **GENETIC DEFECTS IN INSULIN ACTION**
- **OTHER GENETIC SYNDROMES ASSOCIATED WITH DIABETES**—Down's, Klinefelter's, Turner's, Wolfram's, Prader-Willi
- **DISEASES OF THE EXOCRINE PANCREAS**—cystic fibrosis, hemochromatosis, neoplasia, pancreatitis, pancreatectomy
- **ENDOCRINOPATHIES**—acromegaly, Cushing's syndrome, glucagonoma, hyperthyroidism, pheochromocytoma
- **INFECTIONS**—congenital rubella, CMV
- **UNCOMMON FORMS OF IMMUNE-MEDIATED DIABETES**
- **DRUG OR CHEMICAL INDUCED**—atypical antipsychotics, corticosteroids, nicotinic acid, pentamidine, phenytoin, protease inhibitors, thiazides

PATHOPHYSIOLOGY

CHRONIC COMPLICATIONS OF DIABETES

- **MACROVASCULAR DISEASE**—patients with diabetes have a 2–4× ↑ in cardiovascular complications (coronary artery disease, stroke/TIA, peripheral vascular disease)
- **RETINOPATHY**
  - **BACKGROUND**—microaneurysms, dot and blot hemorrhages, hard exudates
  - **PRE-PROLIFERATIVE**—soft exudates, macular edema, intra-retinal microvascular abnormality

PATHOPHYSIOLOGY (CONT'D)

  - **PROLIFERATIVE**—increased new vessels around the optic disc, vitreous hemorrhage, detached retina, neovascular glaucoma
- **NEPHROPATHY**—glomerular basement membrane thickening, ↑ glomerular pressure, microalbuminuria, overt proteinuria, nephrotic range proteinuria, end-stage renal disease
- **NEUROPATHY** (50% of all patients)
  - **MONONEUROPATHY**—cranial (III [commonly sparing pupil], IV, VI, VII), peripheral (median, ulnar, peroneal)
  - **MONONEURITIS MULTIPLEX**—combination of multiple mononeuropathies
  - **DISTAL SYMMETRIC POLYNEUROPATHY**—most common with classic stocking-glove distribution. Progressive loss of distal sensation due to axonal loss, followed by motor weakness and motor axonal loss. May be associated with Charcot foot
  - **PROXIMAL POLYNEUROPATHY**—also known as diabetic amyotrophy, diabetic polyradiculopathy, diabetic radiculoplexopathy, or Bruns-Garland syndrome. Usually involving L2–4 roots causing painful, asymmetric, proximal weakness in knee extension, hip flexion, and, importantly, hip adduction (obturator nerve involvement, distinguishing feature from femoral neuropathy)
  - **AUTONOMIC NEUROPATHY**—postural hypotension, gastroparesis, constipation, diarrhea, erectile dysfunction, atonic bladder, hypoglycemia unawareness, hyperhidrosis of upper extremities, anhidrosis of lower extremities, dry skin

REASONS WHY BLOOD GLUCOSE MAY FLUCTUATE

- **LIFESTYLE**—diet (quantity/quality, timing), exercise
- **INSULIN**—injection site, technique, dose

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PATHOPHYSIOLOGY (CONT'D)

- **ILLNESS**—infections, stress
- **NEUROPATHY**—hypoglycemic awareness, gastroparesis
- **DECREASED INSULIN REQUIREMENT**—renal failure, Addison's
- **MEDICATIONS**—interactions
- **BLOOD GLUCOSE TESTING**—accuracy, timing
- **OTHER ENDOCRINE CAUSES OF HYPERGLYCEMIA**—Cushing's, pheochromocytoma, hyperthyroidism

PRECIPITATING FACTORS FOR DKA—infection, insulin omission, myocardial infarction, new-onset diabetes, acute abdomen

CLINICAL FEATURES

HISTORY—**duration** and **type** of diabetes, **diabetic control** (frequency of monitoring, hypoglycemia [± awareness of adrenergic symptoms], hyperglycemia, previous HbA1C, previous DKA/hyperosmolar hyperglycemic state, prior hospitalization), **treatment** (insulin, oral hypoglycemic agents, healthy eating guidelines, exercise, education), **acute complications** (polyuria, polydipsia, blurred vision, numbness, weight loss, fatigue), **chronic complications** (see previous section). Risk factors for heart disease (hyperlipidemia, hypertension, smoking, family history of early cardiac events, obesity)

PHYSICAL—weight, BMI, vitals, fundi (diabetic or hypertensive retinopathy, cataracts), thyroid, chest, cardiac, abdominal examination, insulin injection sites (lipoatrophy or lipohypertrophy), peripheral pulses, check for carotid and femoral bruits, diabetic foot examination including neurological examination

EXAMINATION OF LOWER EXTREMITIES

- **INSPECTION**—shoes, diabetic dermopathy, dry atrophic skin, fissures, callus, necrobiosis lipoidica diabeticorum, muscle atrophy, hair loss, pallor, ulcers (arterial, neuropathic, venous stasis), gangrene (look between toes), dystrophic nails, ingrown nails, fungal nail infections, Charcot foot (neuropathic arthropathy, characterized by collapse of the arch of the midfoot and bony prominences in distinctive places, acute painless episodes of swelling and erythema over ankle or foot)

CLINICAL FEATURES (CONT'D)

- **PALPATION/CIRCULATION**—peripheral pulses, temperature, capillary refill, Buerger's test, ankle/brachial index
- **NEUROLOGICAL**—10 g sensory monofilament, vibration, glove and stalking sensory loss (light touch, pain, temperature), power (dorsiflexion, plantar flexion), ankle reflex

INVESTIGATIONS

BASIC

- **LABS**—glucose, lytes, anion gap, osmolality, ketones, creatinine, urea, HbA1C, fasting lipids, ALT, ALP, CK, TSH, C-peptide, urine albumin to creatinine ratio

SPECIAL

- **ANTIBODIES**—insulin antibody, GAD65 antibody, islet cell antibody

Related Topics
Autonomic Neuropathy (p. 373)
Coronary Artery Disease (p. 28)
Gastroparesis (p. 126)
Gestational Diabetes (p. 474)
Osteomyelitis (p. 277)
Peripheral Neuropathy (p. 371)
Peripheral Vascular Disease (p. 62)

DIAGNOSTIC ISSUES

DIAGNOSTIC CRITERIA FOR DIABETES

	Fasting BG	OGTT (75 g, 2 h)	HbA1C
Normal	<5.6 mmol/L [<100 mg/dL]	<7.8 mmol/L [<140 mg/dL]	<5.5%
Prediabetes[a]			6.0–6.4%
Impaired fasting Glucose	6.1–6.9 mmol/L [110–125 mg/dL]		
Impaired glucose tolerance		7.8–11.0 mmol/L [140–199 mg/dL]	
Diabetes[b]	≥7.0 mmol/L [≥126 mg/dL]	≥11.1 mmol/L [≥200 mg/dL]	≥6.5%

BG blood glucose, *OGTT* oral glucose tolerance test

[a]If fasting BG 5.6–6.0 mmol/L [100–109 mg/dL] and/or HbA1C 5.5–5.9%, consider further testing with 75 g OGTT

[b]Random glucose ≥11.1 mmol/L [≥200 mg/dL] accompanied by classical symptoms (polyuria, polydipsia, unexplained weight loss) also sufficient for diagnosis. In the absence of compatible symptoms, a single laboratory test in the diabetes range should be repeated with a confirmatory test on another day

DIAGNOSTIC ISSUES (CONT'D)

FACTITIOUS LABORATORY ABNORMALITIES—DKA itself may cause ↑ WBC, ↓ Na (correct for glucose), and ↑ amylase, which should correct with resolution of DKA

ACUTE MANAGEMENT OF DIABETIC KETOACIDOSIS

ACUTE—**ABC**, O_2, IV, may need intubation

CORRECT ACID/BASE ELECTROLYTES ABNORMALITIES

- **MONITOR**—continuous cardiac monitor until patient is stable. Create flow sheet with time vs. lytes, anion gap, glucose, insulin, IV fluids, urine output. Careful monitoring and frequent reassessment is required
- **HYDRATION**—NS 15–20 mL/kg IV bolus (~1 L) then 4–14 mL/kg/h (~250–500 mL/h) to fluid resuscitate then decrease IV accordingly
- **POTASSIUM**—once serum K is <5.0 mEq/L and patient is voiding, add supplemental potassium (see table on next page)
- **INSULIN**—give 0.1–0.15 units/kg of regular insulin IV push, then 0.1 units/kg/h (mix 25 units of regular insulin in 250 mL D5W. One unit of insulin is equal to 10 mL of drip). Titrate insulin drip against anion gap. If anion gap still ↑, increase the rate (see table on next page). Try to keep glucose between 10 and 15 mM in first day. As anion gap falls, decrease insulin drip. Switch to SC insulin when (1) anion gap normalized, (2) insulin requirements reasonable, (3) patient hungry, and (4) only in AM (to facilitate monitoring over the course of the day). Ensure overlap of SC insulin with insulin infusion by at least 1–2 h
- **GLUCOSE**—once serum glucose is less than 15 mM, add glucose to IV fluids (e.g., D5NS, D5½NS). If patient is euvolemic and serum sodium is normal or high, D5½NS should be used
- **BICARB**—if pH <6.9, may be beneficial to give 1–2 amps of HCO_3 over 1–2 h. If pH 6.9–7.0, giving HCO_3 is optional. If pH >7.0, giving HCO_3 not necessary
- **PHOSPHATE**—no indication for replacement in the acute setting unless there is severe cardiac/respiratory depression, or when serum phosphate <0.65 mmol/L [2.0 mg/dL]
- **LABS**—obtain hourly lytes, bicarb, anion gap (calculated using measured Na+), glucose. Cerebral edema is a concern (particularly in children) if osmolality/sodium parameters are corrected too quickly. Avoid correcting blood glucose by >5 mmol/L/h [>90 mg/dL/h] or Na + by >0.3–0.5 mmol/L/h

TREAT PRECIPITATING FACTOR(S)

ACUTE MANAGEMENT OF DIABETIC KETOACIDOSIS (CONT'D)

AN EXAMPLE OF AN APPROACH TO THE MANAGEMENT OF DKA

	Hour 1	Hour 2	Hour 3–4	Hour 4–8	Hour 8–24
Hydration	1 L NS	500 mL/h NS	500 mL/h NS	250 mL/h NS	125 – 250 mL/h D5½ NS
IV #1 NS or ½ NS ± potassium replacement	Use ½NS if corrected Na >145 mmol/L (for every 10 mmol/L [182 mg/dL] ↑ in blood glucose, correct Na by ↑ 3 mmol/L)			When glucose <15 mmol/L [<270 mg/dL], change IV to D5½ NS @ 250 mL/h (if corrected sodium is low, use D5NS). If glucose <15 mM [<270 mg/dL], but AG still ↑, run D10W at 80 mL/h so that IV insulin can be ↑	
Insulin	Bolus 0.1 units/kg regular IV insulin (e.g., 7 units for 70 kg)	Continue IV insulin Expect a glucose fall of 5 mmol/h [90 mg/dL/h] Titrate insulin against AG. Double dose if poor response	When glucose <15 mM [<270 mg/day], decrease IV to 2 – 4 units/h, but continue IV until ketosis cleared; use following scale:		After ketoacidosis has cleared, switch to SC insulin and then stop IV insulin
IV #2 Mix 25 units reg insulin in 250 ml D5W (1 unit =10 mL)	Then 0.1 units/kg/h initially following bolus (e.g., 5–10 units/h) Hold for 2 h if hypotensive or K <3.5 mEq/L Target glucose 10–15 mmol/L				Usually keep IV insulin for first day; do not stop overnight

Glucose mM	mg/dL	Insulin drip
<5	<90	Stop and recheck in 1 h
5.1–10	91–180	Decrease by 1 units/h
10.1–15	181–270	No change
15.1–20	271–360	Increase by 1 units/h
20.1–24	361–437	Increase by 2 units/h
>24	>438	Increase by 3 units/h and call MD

If glucose drops by more than 5 mM [90 mg/dL] in 2 h, decrease insulin to 0.5 units/h and call MD

ACUTE MANAGEMENT OF DIABETIC KETOACIDOSIS (CONT'D)

	Hour 1	Hour 2	Hour 3–4	Hour 4–8	Hour 8–24
Potassium replacement (when voiding)	Serum potassium, potassium replacement	<3 mmol/L, give 40 mmol/h	3–4 mmol/L, give 30 mmol/h	4–5 mmol/L, give 20 mmol/h	5–6 mmol/L, give 10 mmol/h
Laboratory	Baseline: glucose, β-OH-butyrate, ABG, urinalysis, CBCD, electrolytes, Cr, PO_4, Mg, ± lipase, CXR, cultures, troponin, ECG	Glucose (C/S), lytes (VBG) ABGs if pH <7.0	Glucose (C/S), lytes (VBG) ABGs if pH <7.0	Glucose (C/S) hourly, lytes (VBG), PO_4	Glucose (C/S) q1–2 h Lytes q4–8 h
Alkaline replacement		Rarely indicated unless severe acidosis (pH <6.9) with incipient circulatory collapse Dose 50–100 mEq, $NaHCO_3$ in ½NS over 30–60 min Extra potassium may be needed with bicarbonate therapy			
Phosphate replacement		Consider if serum phosphorus <0.65 mmol/L [<2.0 mg/dL] and give if serum phosphorus <0.35 mmol/l/h [<1.1 mg/dL] 2.5–8 mmol/l/h [8–25 mg/dL] (1 mmoL of phosphate = 31 mg of elemental phosphorus) (e.g., 10 mL of KPO_4 in 1 L NaCl over 6 h (30 mM PO_4, 44 mEq K)			
General measures		Make flow sheet (ABG's, glucose, lytes, bicarb, AG, ±O_2, urine output), q1h vitals NG tube if unconscious, antibiotics if infection, cardiac monitor when acidotic, give fluid (6–8 L deficit) Foley to urometer if no urine for 4 h			

NOTE: this table should not replace individualized care and sound clinical judgment

Abbreviations: *ABG* arterial blood gas, *AG* anion gap, *CBCD* CBC and differential, *C/S* chemstrips, *NS* normal saline, *VBG* venous blood gas

SPECIFIC ENTITIES

HYPEROSMOLAR HYPERGLYCEMIC STATE

- **PATHOPHYSIOLOGY**—may occur with severe uncontrolled hyperglycemia in type 2 diabetes
- **CLINICAL FEATURES**—characterized by profound dehydration, hyperosmolar state, severe elevation in blood glucose along with hypernatremia. Ketones may be absent (or mildly elevated). Patients often present with neurological deficit (decreased level of consciousness, coma)
- **TREATMENTS**—fluid resuscitation along with an insulin IV drip. Need to correct Na for elevated glucose (add 3 mEq/L to the serum Na for every rise of 10 mmol/L [182 mg/dL] of glucose above 10 mmol/L [182 mg/dL]. To minimize risk of cerebral edema, serum Na should ideally drop by no more than 8–10 mmol/L/day, serum osmolality should drop by no more than 3 mmol/kg/h, and glucose should drop by no more than 3 mmol/L/h. Lower insulin requirement compared to DKA. Mortality 10–20%

LONG-TERM MANAGEMENT

RISK REDUCTION ★ABCDEFG★

- **ASA/ACE INHIBITOR/ARB**—*ASA* 81 mg PO daily for secondary prevention, controversial for primary prevention. ACE inhibitor or ARB should be started if microalbuminuria or hypertension
- **BLOOD PRESSURE CONTROL**—first-line therapy is ACE inhibitor/ARB. Aim for <130/80 mmHg
- **CHOLESTEROL CONTROL**—target LDL <2.0 mmol/L [<77 mg/dL]. Consider statin [HMG-CoA reductase inhibitor] in patients ≥40-years old, or in patients with diabetes of >15 years duration and >30-years old, or in those with established microvascular/macrovascular disease. May consider ezetimibe (↓ LDL), fibrates (↓ triglycerides, ↑ HDL), and/or bile acid sequestrants (↓ LDL) as add-on therapy
- **CARDIOVASCULAR DISEASE SCREENING**—patients should have the following tests done at baseline if they meet any of the following criteria:
  - **ECG**—if age >40, have had diabetes for >15 years, or if they have hypertension, proteinuria, reduced pulses or vascular bruits
  - **EXERCISE ECG STRESS TEST**—angina, atypical chest pain, dyspnea, abnormal ECG, peripheral artery disease, carotid bruits, transient ischemic attack, and stroke
  - **STRESS MIBI**—individuals with an abnormal ECG (LBBB or ST-T wave changes) or who cannot exercise
  - **REVASCULARIZATION**—prompt revascularization vs medical therapy for stable ischemia seems to have similar outcomes (death and major cardiovascular events)

LONG-TERM MANAGEMENT (CONT'D)

- **DIABETIC CONTROL**—individualize treatment targets. **Aim for HbA1C ≤7.0% in most patients**. A target HbA1C of ≤6.5% may be considered in selected patients with type 2 diabetes to reduce risk of microvascular complications. Consider HbA1C of 7.1–8.5% in patients with limited life expectancy, high-level of functional dependency, extensive coronary artery disease, multiple comorbidities, or history of severe hypoglycemia. Target fasting/pre-prandial blood glucose 4.0–7.0 mmol/L [73–126 mg/dL], and 2 h postprandial blood glucose 5.0–10.0 mmol/L [91–182 mg/dL] (or 5.0–8.0 mmol/L [91–145 mg/dL] if HbA1C targets are not met). Diabetes Control and Complications Trial showed that intensive glycemic control of patients with type 1 diabetes reduces retinopathy, nephropathy, and neuropathy. HbA1C correlates with complications. Major side effects include 3× ↑ in hypoglycemia (especially previous episodes, hypoglycemia unawareness) and increased weight gain
- **EDUCATION**—all patients should attend diabetes classes
- **EXERCISE**—150 min per week of moderate to vigorous aerobic physical activity and resistance exercise 3 times per week. Baseline ECG advisable
- **EYE/NEUROLOGIC**—all patients with type 2 diabetes should be referred to an ophthalmologist at the time of diagnosis and then annually. Patients with type 1 diabetes may have a baseline eye assessment 5 years after the diagnosis as long as they are aged 15 or greater. Eye exams may be done annually after that. All patients should have an annual assessment of neuropathy including the diabetic foot exam. Duloxetine, gabapentin, or pregabalin may be used for painful neuropathy. Domperidone, metoclopramide, or erythromycin may be used for gastroparesis
- **FAT REDUCTION** (lose 5–10 kg)—all patients should follow healthy eating guidelines and try to attain an ideal body weight. See OBESITY ISSUES (p. 457)
- **GET GOING TO QUIT SMOKING!**—there are many different options for patients, including nicotine gum, nicotine inhaler, Nicoderm patch, Bupropion SR, and varenicline. Smoking cessation classes

ORAL HYPOGLYCEMIC AGENTS

BIGUANIDES (↓ hepatic glucose production, ↑ tissue insulin sensitivity)—*metformin* 500–1,000 mg PO BID; adverse effects include GI upset and possible lactic acidosis; contraindications

ORAL HYPOGLYCEMIC AGENTS (CONT'D)

include hypoxia, hepatic failure, severe renal failure, HF, poor LV function; hold before giving IV contrast and 48 h post-contrast

SULFONYLUREA (↑ insulin release)— *gliclazide* [Diamicron] 80 mg PO daily to 160 mg BID; *gliclazide* [Diamicron MR] 30–120 mg PO daily; *glimepiride* 1–8 mg PO daily, *glyburide* 2.5–10 mg PO BID; adverse effects include hypoglycemia

MEGLITINIDE (↑ pancreatic insulin release)—*repaglinide* 0.5–4 mg PO TID ac meals; adverse effects include hypoglycemia

DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS—*sitagliptin* 25–100 mg PO daily; *saxagliptin* 2.5–5 mg PO daily. Usually add-on therapy to metformin. Increases incretin levels, increases insulin release in response to glucose, and decreases glucagon resulting in improved postprandial control; weight neutral; long-term adverse effects are not yet known

GLUCAGON-LIKE PEPTIDE-1 (GLP-1) ANALOGUES—*liraglutide* 0.6–1.8 mg SC daily; *exenatide* 5–10 μg SC BID 30 min before meals. Usually add-on therapy. Causes dose-dependent

ORAL HYPOGLYCEMIC AGENTS (CONT'D)

and glucose-dependent insulin secretion, delays gastric emptying, promotes weight loss, and suppresses glucagon. Long-term adverse effects are unknown. Nausea is a common adverse effect and pancreatitis has been reported

SODIUM-GLUCOSE COTRANSPORTER 2 (SGLT2) INHIBITORS—*canagliflozin* 100–300 mg PO daily; *dapagliflozin* 5–10 mg PO daily. Promotes renal excretion of glucose. Increased risk of urinary tract infections vulvovaginal candidal infections

THIAZOLIDINEDIONES (↑ tissue insulin sensitivity, ↓ hepatic glucose production)—*pioglitazone* 15–45 mg PO daily. Adverse effects include hepatotoxicity and fluid retention, contraindications include liver failure, fluid overload, HF, and CAD; avoid concurrent use of insulin and thiazolidinediones as increased fluid retention

α-GLUCOSIDASE INHIBITOR (↓ glucose absorption)—*acarbose* 25–100 mg TID ac meals; adverse effects include bloating and diarrhea

Principles of Insulin Use

NEJM 2005 352:2

STARTING INSULIN FOR NEW PATIENTS

CALCULATE TOTAL DAILY DOSE

- **STABLE PATIENTS**—in type 1 diabetes, total daily dose of insulin is approximately 0.5 units/kg/d (but may be ↑ with insulin resistance [puberty, obesity, pregnancy], or ↓ with residual β-islet cell function or illness [renal failure, Addison's]). In type 2 diabetes, insulin dosages vary greatly; common starting dose is bedtime insulin (intermediate- or long-acting) at 0.1–0.2 units/kg/day (minimum 10 units) to improve control
- **BASAL-BOLUS REGIMENS**—multiple daily injections or continuous subcutaneous insulin infusion (insulin pump) is ideal for patients with type 1 diabetes to achieve good control. Treatment must be individualized. With multiple daily injections, approximately 50% of total insulin is given as basal (intermediate- or long-acting) either once daily (e.g., at bedtime) or BID (e.g., morning and bedtime). Remaining 50% is given as bolus (rapid- or short-acting) with 15–20% before each meal (breakfast, lunch, supper). With continuous subcutaneous insulin infusion (insulin pump) therapy, rapid-acting insulin is used for both basal and bolus components. Initial

STARTING INSULIN FOR NEW PATIENTS (CONT'D)

dosing and subsequent adjustments should be performed under the supervision of a physician familiar with insulin pump technology

- **TWO-THIRDS, ONE-THIRD RULE**—if a patient is unable to comply with multiple daily injections, consider simplified "two-thirds, one-third rule." Provides a rough estimate of the amount of insulin required. Morning dose (given before breakfast) = 2/3 of total daily insulin (2/3 = intermediate acting, 1/3 = short acting), supper dose = 1/3 of total daily insulin (2/3 = intermediate acting, 1/3 = short acting)

SPECIAL CONSIDERATIONS

- **PERI-PROCEDURAL**—patients may sometimes be NPO for tests/procedures/surgeries. Insulin dosing strategies vary widely. Commonly, mealtime (rapid- or short-acting) insulin held when NPO; basal insulin (intermediate- or long-acting) reduced by 20–30% the evening before and on the morning of the test/procedure/surgery
- **RENAL FAILURE**—insulin is renally metabolized, thus its dose must be reduced in patients with renal failure

STARTING INSULIN FOR NEW PATIENTS (CONT'D)

- **METFORMIN AND INSULIN**—consider the use of metformin in conjunction with insulin in type 2 diabetics to increase insulin sensitivity and decrease insulin requirements
- **THIAZOLIDINEDIONES AND INSULIN**—avoid using thiazolidinediones (e.g., rosiglitazone) in combination with insulin as both medications promote fluid retention
- **β-BLOCKERS**—non-selective β blockers may mask signs and symptoms of hypoglycemia. Consider use of cardioselective β-blocker agents instead

REGULAR INSULIN DOSE ADJUSTMENT PRINCIPLES

INSULIN ADJUSTMENTS—understanding the pharmacokinetics of different insulin types is essential. Blood glucose is checked 4 times/day, before meals and at bedtime

- **HIGH AM BLOOD GLUCOSE**—check 3 AM glucose. If there is nocturnal hypoglycemia, bedtime basal insulin should be decreased. If the 3 AM glucose is elevated, bedtime basal insulin should be increased
- **HIGH LUNCH TIME BLOOD GLUCOSE**—should increase breakfast mealtime insulin dose
- **HIGH SUPPER TIME BLOOD GLUCOSE**—should increase noon mealtime insulin dose or morning basal dose
- **HIGH BEDTIME BLOOD GLUCOSE**—should increase supper insulin mealtime dose

INSULIN-CARBOHYDRATE RATIO—in type 1 diabetes, meal-time insulin can be dosed according to the content of the meal. Insulin-carbohydrate ratio is the number of grams of carbohydrate that 1 unit of rapid-acting insulin will cover. Average ratio is 1:10–1:15, but must be individualized for each patient. Ratios are empirically derived and vary from person-to-person and may also vary from meal-to-meal. Matching insulin dosage with the amount of carbohydrate consumed allows for greater flexibility around meals (e.g., if insulin-carbohydrate ratio is 1:10 and meal contains 90 g of carbohydrate, then 9 units of rapid-acting insulin should be taken). However safe use of insulin-carbohydrate ratios requires that the patient has learned, understands, and can accurately apply carbohydrate counting

INSULIN-SENSITIVITY FACTOR (CORRECTION FACTOR)—in type 1 diabetes, a correction factor can be used to estimate the amount the blood glucose expected to drop with 1 unit of rapid-acting insulin. Applying correction factor at mealtimes can help achieve desired blood glucose

REGULAR INSULIN DOSE ADJUSTMENT PRINCIPLES (CONT'D)

targets. Correction factor is estimated by 100 divided by total daily dose of insulin (e.g., if sum of basal and bolus insulin over 24 h is 50 units, then total daily dose is 50, and correction factor is $100 \div 50 = 2$; therefore, for every 1 unit of rapid-acting insulin, the blood glucose is expected to ↓ by 2 mmol/L). Correction dose of insulin is calculated by "(measured blood glucose – target blood glucose) ÷ correction factor" (e.g., if pre-meal blood glucose is 10 mmol/L and the target blood glucose is 6 mmol/L, then $[10–6] \div 2 = 2$ units; therefore, 2 units of rapid-acting insulin is expected to ↓ blood glucose from 10 to 6 mmol/L)

COMBINING INSULIN-CARBOHYDRATE RATIOS WITH INSULIN-SENSITIVITY FACTOR—total amount of bolus (rapid-acting) insulin that should be administered at mealtime is the sum of the insulin required for the carbohydrate content of the meal (based on the insulin-carbohydrate ratio) and the correction dose (based on the insulin-sensitivity factor)

TYPES OF INSULIN

Insulin type/action	Trade names
Rapid-acting (clear) Onset: 10–15 min Peak: 1–1.5 h Duration: 3–5 h	Humalog (insulin lispro) NovoRapid (insulin aspart) Apidra (insulin glulisine)
Short-acting (clear) Onset: 30 min Peak: 2–3 h Duration: 6.5 h	Humulin-R Novolin ge Toronto
Intermediate-acting (cloudy) Onset: 1–3 h Peak: 5–8 h Duration: up to 18 h	Humulin-N Novolin ge NPH
Long-acting basal insulin analogues (clear) Onset: 90 min Duration: up to 24 h	Insulin detemir (Levemir) Insulin glargine (Lantus)
Premixed Premixed regular insulin-NPH (cloudy) Premixed insulin analogues (cloudy)	Humulin 30/70 Novolin ge 30/70 Novolin ge 40/60 Novolin ge 50/50 Humalog Mix 25 Humalog Mix 50 Novo Mix 30

Canadian Diabetes Association Guidelines 2013

TREATMENT ISSUES

LOCAL COMPLICATIONS OF INSULIN INJECTION—lipoatrophy (human insulin), lipohypertrophy (animal insulin), edema, itching, pain or warmth at injection site, scar tissue

TREATMENT ISSUES (CONT'D)

LONG-TERM COMPLICATIONS OF INSULIN USE—weight gain and risk of hypoglycemia. Possible association between long-acting insulin and malignancy has been suggested, however, further studies required

Hypoglycemia

DIFFERENTIAL DIAGNOSIS

↑ **INSULIN AND** ↓ **C-PEPTIDE**—exogenous insulin, insulin autoantibodies
↑ **INSULIN AND** ↑ **C-PEPTIDE**—drugs (sulfonylurea, meglitinide, pentamidine, quinine), β-cell tumor (insulinoma, nesidioblastosis)
↓ **INSULIN AND** ↓ **C-PEPTIDE**—alcoholism, sepsis, adrenal insufficiency, panhypopituitarism, liver failure, HF, renal failure, anorexia, inborn errors of metabolism, drugs (β-blockers, salicylates, haloperidol), starvation (inanition), IGF-II-secreting tumors

PATHOPHYSIOLOGY

DEFINITION OF HYPOGLYCEMIA—plasma glucose <4.0 mmol/L [<72 mg/dL]
REACTIVE HYPOGLYCEMIA—hypersecretion of insulin postprandially (hypoglycemia occurring within 4 h after meals)
CLINICAL PEARL—the most common reason for a patient to have a low glucose is too much insulin or exposure to oral hypoglycemic agents. However, in patients without diabetes who are presenting with hypoglycemia, it is important to rule out alcoholism, severe sepsis, adrenal insufficiency, and panhypopituitarism. Insulinoma is rare and should be a diagnosis of exclusion. Always consider surreptitious use if no obvious cause found, especially if there is possibility of access to diabetic drugs

CLINICAL FEATURES

SYMPTOMS—sweating, palpitations, tachycardia, dizziness, blurred vision, mental deficits, altered level of consciousness

CLINICAL FEATURES (CONT'D)

WHIPPLE'S TRIAD—measured hypoglycemia, corresponding symptoms of hypoglycemia, reversal of symptoms with glucose

INVESTIGATIONS

BASIC

- **LABS**—collected when glucose is low: plasma glucose, insulin, and C-peptide should be sent ± spot urine for sulfonylurea screen. Also send for cortisol, free T4, ketones, liver function studies and renal function. If sepsis is suspected, order CBCD, blood and urine cultures, and CXR

SPECIAL

- **72-h FASTING STUDY**—may help in the diagnosis of insulinoma if spontaneous hypoglycemic episodes are infrequent. Consult endocrinology
- **THIN CUT CT OF PANCREAS WITH PANCREATIC ANGIOGRAM**—if suspect pancreatic tumor
- **OTHER IMAGING MODALITIES**—endoscopic ultrasound, MRI pancreas, and octreotide scan

MANAGEMENT

ACUTE—*glucose tablets* 15 g PO, ensure snack or meal afterward. If hypoglycemia is severe and patient is unresponsive, give D50W IV push and/or *glucagon* 1 mg SC/IM × 1 dose. Monitor chemstrips q1h to ensure glucose normalizes
TREAT UNDERLYING CAUSE

Hypothyroidism

DIFFERENTIAL DIAGNOSIS

PRIMARY HYPOTHYROIDISM

- **THYROIDITIS**—Hashimoto's, subacute, lymphocytic (silent, postpartum), irradiation
- **IATROGENIC**—radioactive I^{131}, thyroidectomy
- **DRUGS**—methimazole, propylthiouracil, iodide (kelp, radiocontrast dyes), lithium, amiodarone
- **CONGENITAL**—thyroid agenesis, thyroid dysgenesis, Pendred syndrome
- **OTHERS**—iodine deficiency (endemic goiter), infiltration (amyloidosis, hemochromatosis, sarcoidosis, Riedel's thyroiditis/IgG4-related disease)

CENTRAL HYPOTHYROIDISM—diseases of the pituitary or hypothalamus (tumor, surgery, infarction, infection, infiltration, irradiation)

CLINICAL FEATURES

HISTORY—fatigue, dry skin, cold intolerance, depression, confusion, memory loss, goiter, constipation, weakness, carpel tunnel syndrome, menorrhagia, amenorrhea, weight gain, medications, family history of thyroid disease

PHYSICAL—bradycardia, bradypnea, diastolic hypertension, hypothermia, cool and dry skin, vitiligo, orange skin (from carotenemia), carpel tunnel syndrome, thinning hair, periorbital edema, anemia, goiter, pleural effusion, pericardial effusion, proximal myopathy, pseudomyotonia, delayed relaxation phase of the reflexes, edema (non-pitting)

INVESTIGATIONS

BASIC

- **LABS—**TSH (see note below regarding free T4 and free T3)

SPECIAL

- **ANTI-TPO ANTIBODY**

DIAGNOSTIC ISSUES

TSH—usually all that is required to make a diagnosis. Free T4 and free T3 not routinely measured. If central hypothyroidism suspected, check TSH with free T4. In sick euthyroid, biochemical lab abnormalities may occur even though patient is clinically euthyroid

DIAGNOSTIC ISSUES (CONT'D)

INTERPRETATION

	TSH	fT4	fT3
Subclinical hypothyroidism	↑	N	N
Primary hypothyroidism	↑	↓	↓
Central hypothyroidism	N/↓	↓	↓
Sick euthyroid syndrome	N/↑/↓	N/↓	↓
Nephrotic syndrome, anticonvulsants (phenytoin, carbamazepine)	N	↓	↓

MANAGEMENT

MYXEDEMA COMA—ABC, O_2, IV. ***Hydrocortisone*** 100 mg IV q6h (**give hydrocortisone first** and until concurrent adrenal insufficiency has been ruled out). ***Levothyroxine*** 200–500 µg IV, then 100 µg IV daily initially (and if IV continued, give 80% of appropriate PO dose, but not more than 1.4 µg/kg of ideal body weight). **Warming blankets.** Important to rule out adrenal crisis as levothyroxine can cause severe decompensation in patients with untreated adrenal insufficiency. Rule out infection

TREAT UNDERLYING CAUSE—***levothyroxine*** (T4) 75–100 µg PO daily (1.6 µg/kg/day). But in elderly or those with heart disease, it is important to initiate treatment at a dose of 25–50 µg PO daily and titrate up by 25 µg increments

TREATMENT ISSUES

SUBCLINICAL HYPOTHYROIDISM—treatment controversial but should be considered if at high risk of progressing to overt hypothyroidism (e.g., significantly ↑ TSH and ↑ TPO-Ab) or planning pregnancy

ADJUSTMENTS—T4 half-life is 7 days. It takes 4–8 weeks for serum TSH to equilibrate after thyroid medication adjustments

FREE T4—should be used to follow treatment progress in patients with secondary hypothyroidism

SPECIFIC ENTITIES

SICK EUTHYROID SYNDROME—in medically sick but clinically euthyroid patients! Secondary to hypothalamic–pituitary axis disruption, with ↓ T4 → T3 conversion. Mildly altered N/↑/↓ TSH, N/↓ total T4, ↓ fT3, ↑ rT3. Thyroid replacement is not needed. Repeat TSH when acute illness resolved

Related Topic
Hypothyroidism in Pregnancy (p. 476)

Hyperthyroidism

NEJM 2007 358:24

DIFFERENTIAL DIAGNOSIS

PRIMARY HYPERTHYROIDISM

- **GRAVES' DISEASE** (diffuse toxic goiter)—most common cause of hyperthyroidism
- **TOXIC ADENOMA/TOXIC MULTINODULAR GOITER**—more common in elderly
- **THYROIDITIS**—subacute thyroiditis, lymphocytic thyroiditis (subacute, postpartum), Hashimoto's thyroiditis ("Hashitoxicosis"), radiation-induced thyroiditis, drug-induced thyroiditis (lithium, amiodarone, interferon)
- **IODINE EXPOSURE**—kelp, seaweed, radiocontrast dye
- **EXOGENOUS**—L-thyroxine ingestion, hamburger thyrotoxicosis
- **ECTOPIC**—struma ovarii (thyroid tissue present in an ovarian tumor), hydatidiform mole

SECONDARY HYPERTHYROIDISM—pituitary TSHoma (rare)

PATHOPHYSIOLOGY

GRAVES' DISEASE—circulating IgG that binds to and activates the TSH receptor, resulting in follicular hyperplasia (diffuse thyroid enlargement) and overproduction of thyroid hormones. As with many other autoimmune disorders, Graves' disease occurs more frequently in women (10:1) and may be precipitated by stress, infections, and recent labor/delivery

CLINICAL FEATURES

HISTORY—fatigue, sweating, heat intolerance, psychosis, agitation, confusion, anxiety, goiter, dyspnea, palpitations, diarrhea, amenorrhea, weight loss, medications, family history. Symptoms may be masked by β-blockers

PHYSICAL—vitals (tachycardia, atrial fibrillation, tachypnea, systolic hypertension, fever), systolic flow murmur, systolic pleuro-pericardial scratch (Means–Lerman scratch), thyroid acropachy (clubbing, Graves' only), onycholysis (Plummer's nails), palmar erythema, tremor, warm and moist skin ("velvet skin"), stare, exophthalmos, proximal myopathy, hyperreflexia, pretibial myxedema (Graves' only), splenomegaly

- **GOITER**—present along with thyroid bruits in Graves'. Thyroid enlargement may be found in other types of hyperthyroidism or hypothyroidism as well
- **GRAVES' OPHTHALMOPATHY**—protrusion of eyes from the orbits. Features include upper and lower lid retraction, lid lag and stare, ophthalmoplegia, diplopia, conjunctivitis, chemosis, corneal ulceration, optic atrophy, loss of vision. Check visual acuity and visual fields, measure exophthalmos with exophthalmometer

CLINICAL FEATURES (CONT'D)

CLASSIFICATION OF GRAVES' OPHTHALMOPATHY ★NO SPECS★

Class	Findings
0	**N**o symptoms or signs
I	**O**nly symptoms of ocular irritation (dryness, grittiness)
II	**S**oft tissue involved (periorbital edema)
III	**P**roptosis
IV	**E**xtraoccular muscle involved (ophthalmoplegia)
V	**C**orneal involvement
VI	**S**ight loss

THYROID STORM—may be precipitated by anesthetics, surgery, trauma, systemic illness (especially sepsis), iodine load, and parturition. Clinical manifestations include fever, CNS (delirium), CVS (tachycardia, hypotension), and/or GI (vomiting, jaundice, diarrhea, ↑ LFT) symptoms. The presence of thyrotoxicosis along with dysfunction in 2 of 4 systems qualifies as thyroid storm

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE A GOITER?

NORMAL—15–20 g. Abnormal if each lateral thyroid lobe has volume greater than the individual's terminal phalanx of thumb

INSPECTION—slightly extend the neck, observe from front and side, observe the patient swallow, measure amount of prominence with a ruler (>2 mm AP diameter on lateral exam below cricothyroid membrane has very high LR+ for goiter; non-visible gland suggests absence of goiter)

PALPATION—locate thyroid isthmus by palpating between cricoid cartilage and suprasternal notch. Feel the left lobe with neck slightly flexed and rotated to left, and then right lobe. Ask patient to swallow sips of water and repeat palpation. Describe the size of the thyroid, its texture, and consistency; comment on the presence or absence of nodules or tenderness

CLINICAL FEATURES (CONT'D)

AUSCULTATION—listen for bruits over each lobe and the isthmus

APPROACH—"perform both inspection and palpation (LR+ 0.15 if normal exam, LR+ 1.9 if 1–2× size, LR+ 25 if >2× size)"

JAMA 1995 273:10
The Rational Clinical Examination. McGraw-Hill, 2009

INVESTIGATIONS

BASIC

- **LABS**—TSH, fT4, fT3, TSH receptor antibody (Graves'), anti-TPO antibody (Hashimoto's), thyroglobulin (↓ if factitious, ↑ if thyroiditis), ESR (↑ if thyroiditis), CBCD, ALT, AST, ALP, bili, ECG

SPECIAL

- **RADIOACTIVE IODINE UPTAKE**—to differentiate between thyrotoxicosis from hyperthyroidism (↑ uptake) vs. thyroiditis (↓ uptake). Normal 2 h uptake = 6–10%; <1% suggests thyroiditis, 1–6% suggests iodine exposure, >10% suggests Graves', toxic nodule, or toxic multinodular goiter
- **THYROID SCAN**—to determine functional status of nodule(s). Diffuse homogeneous increased iodine uptake suggests Graves' disease, multifocal uptake suggests toxic multinodular goiter, increased single focus suggests toxic adenoma, while decreased global uptake suggests thyroiditis or factitious hyperthyroidism and decreased localized uptake may suggest cold nodule

DIAGNOSTIC ISSUES

THYROID HORMONE LEVELS AND INTERPRETATION

	TSH	fT4	fT3
Subclinical hyperthyroidism	↓	N	N
Primary hyperthyroidism	↓	↑	↑
T3 thyrotoxicosis	↓	N	↑
Secondary hyperthyroidism	↑/N	↑	↑

MANAGEMENT

THYROID STORM—ABC, O_2, IV. ***Propylthiouracil*** 1,000 mg PO/NG/PR STAT, then 200 mg PO/NG/PR q4h×1 week then 200 mg PO BID. ***Iodine/iodide*** with *Lugol's solution* 5–10 drops PO q8h or *saturated potassium iodide (SSKI)* 1–2 drops PO q8h, to be given 1 h ***after*** each dose of PTU. ***Glucocorticoids*** with *hydrocortisone* 100 mg IV q8h *or dexamethasone* 2 mg IV q6h. ***Propranolol*** 20–80 mg PO q6h. **Cooling blankets**

TREAT UNDERLYING CAUSE

- **ANTITHYROID DRUGS**—inhibit thyroid hormone synthesis; for Graves', multinodular goiter and toxic adenoma. *Methimazole* 10–30 mg PO daily for most cases of hyperthyroidism, or *propylthiouracil* 50–300 mg PO TID. Methimazole associated with better safety profile, more convenient dosing, and less I^{131} failure rates than propylthiouracil
- **SODIUM IODATE**—potent inhibitor of peripheral T4 conversion and decreases thyroid hormone release
- **β-BLOCKERS**—↓ tissue response to catecholamines and ↓ peripheral conversion of T4 to T3; used as adjunct
- **GLUCOCORTICOIDS**—↓ immune response and ↓ peripheral conversion of T4 to T3; for severe hyperthyroidism
- **RADIOIODINE I^{131} ABLATION**—for Graves', multinodular goiter and toxic adenoma. Give once thyroid levels have been stabilized. Must discontinue antithyroid drugs 3–7 days in advance. Avoid I^{131} if severe ophthalmopathy, smoking, severe thyrotoxicosis, pregnant, or breastfeeding as may make eye disease worse or lead to thyroid storm. Hypothyroidism within 2–4 months is expected. Many develop permanent hypothyroidism and require thyroid hormone replacement (1.6 μg/kg/day)
- **THYROIDECTOMY**—for patients who fail medical therapy, are unable to receive radioactive ablation (e.g., severe ophthalmopathy), have compressive goiter, or have another indication for surgery (e.g., nodule suspicious for malignancy)

TREATMENT ISSUES

PROPHYLTHIOURACIL MECHANISM—inhibits intra-thyroidal organification of iodide and thyroid hormone synthesis. High dosages (≥600 mg) inhibit conversion of T4 to T3. Preferred in pregnancy during first trimester (less teratogenicity vs. methimazole)

SPECIFIC ENTITIES

APATHETIC (MASKED) THYROTOXICOSIS—in the elderly, thyrotoxicosis may manifest as isolated congestive heart failure, unexplained weight loss, or atrial fibrillation without other classical symptoms and signs

SPECIFIC ENTITIES (CONT'D)

THYROIDITIS—subacute thyroiditis is painful whereas silent thyroiditis is painless. Thyroiditis typically leads to hyperthyroidism initially as the thyroid cells lyse, then a period of hypothyroidism before recovering to euthyroid state

Related Topic
Hyperthyroidism in Pregnancy (p. 476)
Amiodarone-associated Thyrotoxicosis (under Important Toxicities of Amiodarone (p. 48)

Solitary Thyroid Nodule

NEJM 2004 351:17

ATA 2009 Differentiated Thyroid Cancer Guidelines
ATA 2009 Medullary Thyroid Cancer Guidelines

DIFFERENTIAL DIAGNOSIS

BENIGN (95%)—colloid nodule, benign follicular neoplasm (adenoma), cyst, thyroiditis
MALIGNANT (5%)—thyroid carcinoma (papillary, follicular, medullary, anaplastic), lymphoma

CLINICAL FEATURES

RISK FACTORS FOR THYROID CANCER

- **CLINICAL RISK FACTORS**—family history of medullar thyroid carcinoma or MEN2, rapid growth, fixated/firm/hard nodule, extremes of age <20 or >60, male sex, prior head and neck irradiation, nodule >4 cm [>1.6 in.] in diameter, symptoms of compression (dysphagia, dysphonia, hoarseness, dyspnea, cough), regional lymphadenopathy, distant metastases, hypothyroidism
- **SUSPICIOUS ULTRASOUND FINDINGS**—hypoechoic lesion, absence of cystic elements, irregular/infiltrative margins, microcalcifications, absence of halo, increased central vascularity, appearance taller than wide on transverse view

INVESTIGATIONS

BASIC

- **LAB TESTS**—TSH
- **IMAGING**—US
- **FNA**—±US-guidance

SPECIAL

- **THYROGLOBULIN LEVEL**—for follow-up of follicular-cell derived thyroid cancer
- **CALCITONIN LEVEL**—for follow-up of medullary thyroid cancer
- **THYROID SCAN**—if hyperthyroidism to determine hot vs. cold nodule

DIAGNOSTIC ISSUES

SIZE CUTOFF FOR EVALUATION—most lesions <1 cm [<0.4 in.] on US do not require FNA, but may be followed over time with a repeat US in 6–12 months. Recommend FNA for nodules ≥1.5–2 cm [≥0.6–0.8 in.], or ≥1 cm [≥0.4 in.] with high-risk features

THYROID FUNCTION AND CANCER RISK—thyroid nodules have a 5–15% risk of being malignant; 1/3 of all nodules are cold and less than 1/3 of cold nodules are malignant. Functioning nodules are usually benign. Cold nodules in the setting of autoimmune thyroid disease also have a higher risk of malignancy

BETHESDA CLASSIFCATION OF FNA BIOPSIES—standardized classification system with six categories: (1) non-diagnostic or unsatisfactory (e.g., cyst fluid only, acellular specimen) with 1–4% risk of malignancy; (2) benign (e.g., benign follicular nodule) with ≤3% risk of malignancy; (3) follicular lesion of undetermined significance or atypia of undetermined significance with 5–15% risk of malignancy; (4) follicular neoplasm or suspicious for follicular neoplasm (e.g., Hurthle cell neoplasm) with 15–30% risk of malignancy; (5) suspicious for malignancy with 50–75% risk of malignancy; and (6) malignant (e.g., papillary, medullary, anaplastic thyroid cancer) with >95% risk of malignancy

MANAGEMENT

INCIDENTAL NODULE <1 CM—usually no further testing required, but may consider repeat US in 6–12 m

INCIDENTAL NODULE 1–4 CM—proceed to FNA. Non-diagnostic biopsies associated with 10–20% risk of malignancy → rebiopsy after 3 months

INCIDENTAL NODULE (>4 CM)—advise surgical removal, especially in younger patients

BENIGN NODULE—follow-up with serial US 6–12 m after initial FNA. If size stable, follow-up

MANAGEMENT (CONT'D)

annually with clinical exam. If size ↑ significantly (e.g., ≥20% with at least ≥2 mm in ≥2 dimensions in solid component), repeat FNA. Consider **thyroidectomy** if there is a pattern of growth or obstructive symptoms, or **radioiodine** if functional nodule

PURELY CYSTIC NODULE—drain if symptomatic, but recurrence common

MALIGNANT NODULE—refer for **total/near-total thyroidectomy** ± possible postoperative **radioactive iodine remnant ablation**

TREATMENT ISSUES

OVERALL APPROACH TO DIAGNOSIS AND TREATMENT

- **LOW TSH**—obtain thyroid scan → functioning nodule → radioiodine; alternatives include no treatment or surgery. If nonfunctioning (cold) nodule, proceed to FNA
- **NORMAL OR HIGH TSH**—if strong suspicion of cancer, proceed to surgery. Otherwise, US-guided FNA → if malignant or suspicious, proceed to surgery. If benign, follow-up clinically → repeat thyroid US in 6–12 months; alternatives include surgery. If non-diagnostic FNA, repeat FNA

Pituitary Tumors NEJM 2003 349:21

DIFFERENTIAL DIAGNOSIS OF PITUITARY TUMORS

FUNCTIONAL—prolactinoma is most common, Cushing's disease (pituitary ACTH-secreting tumor) and acromegaly are rare, functional TSH tumors are exceedingly rare

NON-FUNCTIONAL

OTHER NON-PITUITARY TUMORS—meningioma, craniopharyngioma, dysgerminoma, optic glioma, metastases

DIFFERENTIAL DIAGNOSIS OF HYPERPROLACTINEMIA

PHYSIOLOGIC—pregnancy, lactation, exercise, coitus, stress

TUMORS—pituitary (prolactinoma, other functional tumors [acromegaly], non-functional tumor with stalk compression [macroadenoma]), non-pituitary

DRUGS—metoclopramide, domperidone, phenothiazines, risperidone, TCA, SSRI, labetalol, verapamil, ranitidine, estrogen, opioids

OTHERS—hypothyroidism (↑ TRH), chronic kidney disease, chest wall irritation (trauma, surgery, zoster)

IMPORTANT—prolactin secretion is normally inhibited by dopamine. Therefore, anything that interferes with dopamine secretion/delivery (e.g., pituitary stalk compression) can lead to ↑ prolactin secretion

CLINICAL FEATURES

★GO LOOK FOR THE ADENOMA PLEASE★—A compressive pituitary adenoma usually affects

CLINICAL FEATURES (CONT'D)

hormone secretion in this order: ↓ **G**H, ↓ **L**H and **F**SH, ↓ **T**SH, ↓ **A**CTH, and ↑ **P**rolactin

SYMPTOMS—inquire about hormonal excess, hormonal deficiencies, and mass effect (see below)

MASS EFFECT—visual field abnormalities (bitemporal hemianopsia), blurred vision (↓ visual acuity), headaches, cranial nerve palsies, loss of color (red) discrimination

GROWTH HORMONE DEFICIENCY—nonspecific symptoms (obesity, ↓ exercise capacity, weakness, low mood, fatigue)

GROWTH HORMONE EXCESS (ACROMEGALY)—see SPECIFIC ENTITIES below for details

CORTISOL DEFICIENCY (ADRENAL INSUFFICIENCY)—see section on Adrenal Insufficiency (p. 450) for details

CORTISOL EXCESS (CUSHING SYNDROME)—see section on Adrenal Incidentaloma (p. 448) for details

THYROID HORMONE DEFICIENCY (HYPOTHYROIDISM)—see section on Hypothyroidism (p. 440) for details

THYROID HORMONE EXCESS (HYPERTHYROIDISM)—see section on Hyperthyroidism (p. 442) for details

HYPERPROLACTINEMIA IN ♀—amenorrhea, oligomenorrhea, galactorrhea, infertility, sexual dysfunction, osteoporosis

HYPERPROLACTINEMIA IN ♂—erectile dysfunction, infertility, osteoporosis

LH/FSH DEFICIENCY—hypogonadism

LH/FSH EXCESS—usually silent, sometimes paradoxical hypogonadism

INVESTIGATIONS

BASIC

- **LABS**—prolactin, IGF-1 (simpler than GH to interpret), LH, FSH, TSH, ACTH, AM cortisol, free T4 ± AM testosterone, estrogen, progesterone
- **IMAGING**—MRI pituitary

SPECIAL

- **75-G ORAL GLUCOSE TOLERANCE TEST**—if suspect acromegaly
- **1 MG DEXAMETHASONE SUPPRESSION TEST**—if suspect Cushing's syndrome

DIAGNOSTIC ISSUES

MICROADENOMA (<10 mm [<0.4 in.])**—** evaluate for hormonal hypersecretion (e.g., prolactin, IGF-1, free T4, 1 mg dexamethasone suppression test [or 24 h urinary free cortisol, or late night salivary cortisol])

MACROADENOMA (≥10 mm [≥0.4 in])— evaluate for hormonal hypersecretion (see above) and hyposecretion (e.g., AM testosterone [if ♂], AM cortisol ± LH and FSH [if ♀; may omit if regular menses]). Refer to ophthalmologist for formal visual field testing

HYPERPROLACTINEMIA—if prolactin <2× upper limit of normal, repeat at least two more times (fasting and at rest) as most cases will normalize spontaneously. If persistent ↑ prolactin confirmed, look for potential offending medications, check pituitary function, renal function, liver function, β-hCG (in ♀), TSH, IGF-1, MRI pituitary ± macroprolactin assay

MANAGEMENT

PROLACTINOMA—**dopamine agonists** (*cabergoline* 0.25–1 mg PO 2×/week, *bromocriptine* 1.25–7.5 mg PO BID). **Transsphenoidal surgery** (if resistant to medical therapy or visual field compromise). Indications for treatment include infertility, galactorrhea, hypogonadism, related osteoporosis, mass effect, and macroadenoma

ACROMEGALY—**transsphenoidal surgery** (preferred). See SPECIFIC ENTITIES below for details

CUSHING'S DISEASE—**transsphenoidal surgery**. See p. 399 for details

TSH SECRETING—**transsphenoidal surgery** (first line but cure rates low). Consider **octreotide** and treatment with antithyroid medications as appropriate. See section on Hyperthyroidism (p. 442) for details

MANAGEMENT (CONT'D)

NON-FUNCTIONAL—replace any hormone deficiencies, consider **transsphenoidal surgery** (if symptomatic/mass effect)

SPECIFIC ENTITIES

ACROMEGALY

- **PATHOPHYSIOLOGY**—excessive growth hormone secretion, usually from pituitary adenoma
- **CLINICAL FEATURES**—vitals (hypertension), large, doughy, spade-like hands, increased hand/foot/head size (↑ ring, glove, shoe, and hat size), increased sweating, osteoarthritis (DIP, PIP, CMC, wrists), carpal tunnel syndrome, proximal muscle weakness, coarse facial features, frontal bossing, bitemporal hemianopsia, sleep apnea, wide-spaced teeth, enlarged tongue, hoarse voice, prognathism (prominent mandible), acrochordons (skin tags), acanthosis nigricans (insulin resistance), cardiomegaly with or without HF, enlarged liver/spleen/kidneys, testicular atrophy, foot drop (common peroneal nerve entrapment)
- **DIAGNOSIS**—serum IGF-1. Also check prolactin, TSH, LH/FSH, and AM cortisol. MRI pituitary. 75 g oral glucose tolerance test (serum GH levels remain elevated after 2 h)
- **TREATMENTS**—**transsphenoidal surgery** (preferred, 5–20% recurrence). **Octreotide** (long-acting analogue of somatostatin). **Cabergoline** or **bromocriptine** may be combined with somatostatin analogue. **Pegvisomant** (growth hormone receptor antagonist) if somatostatin analogue ineffective. **Irradiation** of pituitary

ANTERIOR PITUITARY DEFICIENCY

- **CAUSES**—infiltration (tumor, sarcoidosis), infection (TB, actinomycosis), vascular (Sheehan's, apoplexy), autoimmune hypophysitis, inherited/congenital, irradiation
- **CLINICAL FEATURES**—growth failure, deficient or absent lactation, hypogonadism, hypothyroidism, and adrenal insufficiency. In pituitary apoplexy may have severe headache and visual disturbance
- **TREATMENTS**—replace hormone deficiencies, treatment specific to etiology

POSTERIOR PITUITARY DEFICIENCY

- **CAUSES**—infiltration (tumor, sarcoidosis), infection (TB), infarction (Sheehan's), irradiation, iatrogenic (neurosurgery)
- **CLINICAL FEATURES**—diabetes insipidus
- **TREATMENTS**—*desmopressin/DDAVP*—see diabetes insipidus (p. 396) for more details

Polyuria — NEJM 2006 355:24

DIFFERENTIAL DIAGNOSIS

OSMOTIC DIURESIS (~3 L/day, urine osm ~500 mOsm/kg)—glucose, urea, mannitol

WATER DIURESIS (~20 L/day, urine osm <100 mOsm/kg)

- **NEPHROGENIC DIABETES INSIPIDUS**—hypercalcemia, hypokalemia, lithium, demeclocycline, obstructive uropathy, congenital
- **CENTRAL DIABETES INSIPIDUS**—**iatrogenic** (neurosurgery), **granulomatous infiltration** (sarcoidosis, TB, histiocytosis X), **trauma** (closed head injury), **tumor** (craniopharyngioma, metastatic breast cancer, metastatic lung cancer), **autoimmune** (infundibuloneurohypophysitis), **congenital**
- **PSYCHOGENIC POLYDIPSIA**

SALINE DIURESIS (~3 L/day, urine osmo ~300 mOsm/kg)—post-ATN, post-obstructive

PATHOPHYSIOLOGY

DEFINITION OF POLYURIA—urine >3 L/day

INVESTIGATIONS

BASIC

- **LABS**—lytes, urea, Cr, glucose, serum osmolality (if diabetes insipidus, >290 mOsm/kg), 24 h urine volume, urine lytes, urine osmolality (if diabetes insipidus, <275 mOsm/kg)

SPECIAL

- **WATER DEPRIVATION TEST**—consult endocrinology. In the dehydrated state, the body normally concentrates urine, but in diabetes insipidus, the urine remains dilute. Serial measurements of urine output, urine and serum lytes and osmolality, weight. Administration of 1 μg desmopressin/DDAVP IV/SC causes concentration of the urine in central DI but not nephrogenic DI (but unreliable if medullary gradient has been washed-out)
- **MRI PITUITARY**—if central diabetes insipidus

MANAGEMENT OF DIABETES INSIPIDUS

TREAT UNDERLYING CAUSE—**central diabetes insipidus** (*desmopressin/DDAVP* 10–20 μg intranasally daily–BID, or 0.5–2 μg SC/IV daily–BID, or 0.1–1.2 mg PO divided QHS–TID). Goal of treatment is to improve quality of life (↓ polydipsia, ↓ polyuria) while allowing occasional breakthrough. Note risk of hyponatremia

Adrenal Incidentaloma — NEJM 2007 356:6

DIFFERENTIAL DIAGNOSIS

BENIGN

- **FUNCTIONAL ADENOMA**—Cushing's (cortisol-secreting adenoma), Conn's (aldosterone-secreting adenoma), androgen-secreting adenoma
- **NON-FUNCTIONAL ADENOMA**
- **PHEOCHROMOCYTOMA/PARAGANGLIOMA**—may be benign or malignant
- **OTHER**—myelolipomas, hamartomas, granulomas

MALIGNANT

- **CARCINOMA**—adrenocortical carcinoma (may secrete cortisol, aldosterone, and/or androgens)
- **METASTASES**—lung, breast, GI, renal, melanoma

PATHOPHYSIOLOGY

SYMPATHETIC RESPONSE—adrenal medulla produces 85% epinephrine and 15% norepinephrine. Epinephrine has equal effect on *α* and β receptors. Norepinephrine acts mainly on *α* receptors

- **ACTIVATION OF α RECEPTORS**—peripheral vasoconstriction, mydriasis, and sweating
- **ACTIVATION OF β RECEPTORS**—vasodilation, cardiac stimulation, bronchodilation, smooth muscle relaxation

RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM—renin release is stimulated by low blood pressure, low [Na], and the sympathetic nervous system. It causes the activation of angiotensin I, II, and III. Aldosterone release is then stimulated by RAS (AII, AIII), hyperkalemia, and

PATHOPHYSIOLOGY (CONT'D)

ACTH. Aldosterone's effects include increased Na reabsorption and K secretion at the distal tubule

BILATERAL ADRENAL MASSES—occur in 15% of patients with adrenal incidentaloma. Causes include metastatic disease, congenital adrenal hyperplasia, bilateral adrenal adenomas, and infiltrative disease of the adrenals

CLINICAL FEATURES

HISTORY

- **SYMPTOMS OF CUSHING'S**—weight gain, truncal obesity, thin extremities, acne, easy bruising, poor wound healing, emotional and cognitive changes, opportunistic infections, altered reproductive function, hirsutism. Typical symptoms and signs of Cushing's may be minimal or absent with ectopic ACTH production. Hypokalemic alkalosis may be the only obvious initial finding
- **SYMPTOMS OF PHEOCHROMOCYTOMA**—episodic spells of palpitations, pallor, tremor, headache, diaphoresis, hypertension
- **SYMPTOMS OF CONN'S**—hypokalemia, hypertension
- **SYMPTOMS OF ADRENOCORTICAL CARCINOMA**—androgen secretion leading to rapid hirsutism, virilization, acne, amenorrhea
- **PAST MEDICAL HISTORY**—particularly lung, breast, gastrointestinal, and renal cell cancer or melanoma, smoking history

PHYSICAL—vitals (tachycardia, paroxysmal or sustained hypertension, orthostatic hypotension), pallor, tremor, thin skin, purple striae, proximal muscle weakness, hypertensive retinopathy, plethora, acne, hirsutism, supraclavicular and/or dorsocervical fat pad, moon facies, supraclavicular lymphadenopathy, left ventricular hypertrophy, central obesity, abdominal masses

INVESTIGATIONS

BASIC

- **LABS**—1 mg dexamethasone suppression test (or 24 h urine cortisol, or late night salivary cortisol; 8 mg dexamethasone suppression test for ectopic ACTH), lytes, plasma renin and aldosterone (if hypertensive), 24 h urine for metanephrines ± ACTH, DHEAS, androstenedione, testosterone
- **IMAGING**—CT or MRI abdomen

INVESTIGATIONS (CONT'D)

SPECIAL

- **ADRENAL VEIN SAMPLING**—for primary hyperaldosteronism
- **METAIODOBENZYLGUANIDINE (MIBG) SCAN**—for pheochromocytoma
- **IODINE-131-6-B-IODOMETHYL-19-NORCHOLESTEROL (131-I-NP-59) SCAN—**for hypercortisolism/hyperaldosteronism; to determine whether adrenal adenoma functional

DIAGNOSTIC ISSUES

APPROACH TO DIAGNOSIS OF ADRENAL INCIDENTALOMA—always start with history and physical, and baseline labs to determine if tumor is functioning, then proceed with imaging to look for suspicious features suggestive of malignancy

DISTINGUISHING FEATURES OF ADRENAL TUMORS ON CT SCAN

- **ADENOMA**—smooth border, homogeneous density, <4 cm, unilateral, low enhanced attenuation (≤10 Hounsfield Units [HU]), CT contrast-medium wash out ≥50% at 10 min
- **PHEOCHROMOCYTOMA**—cystic, hemorrhagic, variable size, may be bilateral, high enhanced attenuation (>10 HU)
- **ADRENOCORTICAL CARCINOMA**—irregular, heterogeneous density, >4 cm [>1.6 in.], unilateral, high unenhanced attenuation (>10 HU, CT contrast washout <50% at 10 min)
- **METASTATIC DISEASE**—irregular, heterogeneous density, bilateral, high unenhanced attenuation

MANAGEMENT

TREAT UNDERLYING CAUSE—determine functional vs. non-functional tumor and benign vs. malignant tumor. All functional tumors, tumors >4 cm [>1.6 in.], and lesions suspicious for malignancy should be resected

SPECIFIC ENTITIES

MULTIPLE ENDOCRINE NEOPLASIA (MEN) SYNDROMES

- **MEN 1**—pituitary tumor, primary hyperparathyroidism, pancreatic tumor
- **MEN 2A**—pheochromocytoma, medullary thyroid cancer (MTC), primary hyperparathyroidism
- **MEN 2B**—pheochromocytoma, medullary thyroid cancer (MTC), marfanoid

SPECIFIC ENTITIES (CONT'D)

PHEOCHROMOCYTOMA

- **PATHOPHYSIOLOGY**—most predominantly secrete norepinephrine
- **CLINICAL FEATURES**—triad of headaches, palpitations, cold sweats. ★**Rule of 10**★ (a rough simplification): 10% incidental, 10% bilateral/multiple, 10% extra-adrenal, 10% malignant, 10% recurrence after surgery, 10% in children, 10% familial (MEN, VHL)
- **DIAGNOSIS**—24-h urinary metanephrines and creatinine, or plasma fractionated metanephrines
- **TREATMENTS**—**volume repletion** (reduce postural hypotension from adrenergic blockage). **α-blockade** (*phenoxybenzamine* 10 mg PO BID and ↑ dose as needed, or *prazosin* 4–20 mg PO daily in divided doses 2–4 times daily). Consider **β-blockade** only after well *α*-blocked (to control tachycardia and other arrhythmias). Avoid initial β-blockade to prevent unopposed α-constriction. Note that medical therapy should precede surgery by 2 weeks). Refer for **genetic testing**

SPECIFIC ENTITIES (CONT'D)

HYPERALDOSTERONISM

- **PATHOPHYSIOLOGY**—Conn's (primary hyperaldosteronism) can be due to adrenal adenoma or hyperplasia. Secondary hyperaldosteronism can be due to ↑ renin from edematous states, dehydration, diuretics, and renal artery stenosis
- **CLINICAL FEATURES**—hypertension, ↓ K
- **DIAGNOSIS**—↓ renin and ↑ aldosterone for Conn's, ↑ renin and ↑ aldosterone for secondary hyperaldosteronism
- **TREATMENTS**—for unilateral Conn's amenable to surgery, consider adrenalectomy. Otherwise, consider medical therapy (*spironolactone* 12.5–100 mg PO daily–BID or *eplerenone* 25–50 mg PO BID). See Hypertension section for more details (p. 460)

Adrenal Insufficiency

DIFFERENTIAL DIAGNOSIS

PRIMARY

- **AUTOIMMUNE**—Addison's disease
- **INFECTIONS**—TB, histoplasmosis, coccidioidomycosis, AIDS
- **HEMORRHAGE**—anticoagulants, sepsis (Waterhouse–Friderichsen syndrome, associated with meningococcemia), trauma, anticardiolipin antibodies
- **INFILTRATION**—metastases, sarcoidosis, amyloidosis

SECONDARY/TERTIARY—exogenous glucocorticoid therapy, pituitary or hypothalamic tumor (panhypopituitarism), traumatic brain injury, infarction, infection, infiltration, irradiation, drugs (high dose progestins, opiates), idiopathic

CLINICAL FEATURES

HISTORY—fatigue, weight loss, abdominal pain, N&V, postural lightheadedness (presyncope), muscle weakness, hypoglycemia, dehydration, salt cravings (Addison's only), hyperpigmentation (Addison's only), visual field changes (pituitary tumor), evidence of steroid use, medical history (TB, cancer, sarcoidosis), medications (anticoagulation)
PHYSICAL—orthostatic hypotension, hyperpigmentation (Addison's only)

CLINICAL FEATURES (CONT'D)

DISTINGUISHING FEATURES BETWEEN PRIMARY AND SECONDARY/TERTIARY ADRENAL INSUFFICIENCY

	Primary	Secondary/ tertiary
Affected hormones	Cortisol, DHEAS, aldosterone	Cortisol, DHEAS
ACTH	↑	↓
Electrolytes	↓ Na, ↑ K	↓ Na
Symptoms	Hyperpigmentation	Normal skin pigment. GI symptoms and hypotension less prominent

INVESTIGATIONS

BASIC

- **ACTH STIMULATION TEST**—see below
- **LABS**—CBCD, lytes, glucose, urea, creatinine, TSH, free T4
- **MICROBIOLOGY**—blood and urine cultures if suspect sepsis

DIAGNOSTIC ISSUES

ACTH STIMULATION TEST

- **STANDARD DOSE**—obtain cortisol and ACTH at baseline, give cosyntropin 250 μg IV push, measure cortisol at 30 and 60 min. Peak cortisol >550 nmol/L excludes most cases of adrenal insufficiency (but may be misleadingly normal if new-onset disease)

MANAGEMENT

ACUTE ADRENAL CRISIS—ABC, O_2, IV fluids (NS or D5NS 2–3 L IV bolus) and glucose as needed. **Corticosteroid** (*hydrocortisone* 100 mg IV q6-8 h or *dexamethasone* 4 mg IV q6h. **Treat precipitant LONG-TERM TREATMENT—physiologic replacement** (*hydrocortisone* 10–20 mg PO qAM and 5–10 PO qPM or *prednisone* 5 mg PO qAM and 2.5 mg PO qPM, plus *fludrocortisone* 0.1 mg PO daily [if primary adrenal insufficiency]). Advise **medical alert bracelet** and **sick day management ± emergency prefilled hydrocortisone syringe**

STRESS DOSE REPLACEMENT (Prevention)—if patients have been taking suppressive dose of glucocorticoids for >3 weeks during the preceding year, consider stress dosing during illnesses or surgical procedures

- **MINOR STRESS** (e.g., flu, procedure under local anesthetic)—double to triple the regular dose of glucocorticoids
- **MODERATE STRESS** (e.g., orthopedic surgery, perivascular surgery)—*hydrocortisone* 25 mg IV q8h × 3 doses with first dose on call to OR, then resume normal dose
- **HIGH STRESS** (e.g., intraabdominal operations, cardiac surgery)—*hydrocortisone* 50 mg IV q8h × 3 doses with first dose on call to OR, then 25 mg IV q8h × 3 doses, then resume normal dose

Cushing's Syndrome

Endocrine Society 2008 Cushing's Syndrome Guidelines

DIFFERENTIAL DIAGNOSIS

IATROGENIC (↓ ACTH)
PITUITARY (↑ ACTH)—Cushing's disease
ECTOPIC (↑ ACTH)—small cell lung cancer, bronchial carcinoids, neuroendocrine tumors
ADRENAL (↓ ACTH)—adenoma, carcinoma

CLINICAL FEATURES

SIGNS AND SYMPTOMS OF CUSHING'S SYNDROME

- **NEUROLOGICAL**—euphoria, depression, psychosis, restlessness, irritability, insomnia
- **OPHTHALMIC**—glaucoma, cataracts
- **CARDIOVASCULAR**—hypertension, fluid retention
- **GASTROINTESTINAL**—gastritis, ulcers, GI bleed
- **HEMATOLOGICAL**—leukocytosis, immunosuppression
- **ENDOCRINE**—hyperglycemia, insulin resistance, hypogonadism, menstrual irregularity, central obesity, hirsutism, weight gain, osteoporosis
- **MUSCULOSKELETAL**—osteoporosis, avascular necrosis, proximal myopathy
- **DERMATOLOGICAL**—purple striae, moon face, supraclavicular and/or dorsocervical fat pad, skin thinning, easy bruising, acne, poor wound healing

CLINICAL FEATURES (CONT'D)

Note that typical symptoms and signs of Cushing's may be absent or minimal with ectopic ACTH production. Hypokalemic alkalosis may be the only obvious initial finding

INVESTIGATIONS

BASIC

- **LABS**—begin initial evaluation with 1 of 3 possible screening tests (24 h urine cortisol, 1 mg overnight dexamethasone suppression test, or late night salivary cortisol), ACTH, CBCD, lytes, urea, Cr, glucose, HbA1C, fasting lipid profile

SPECIAL

- **CT ADRENAL**—unilateral mass suggests adrenal lesion. Bilateral adrenal hyperplasia suggests ACTH oversecretion (central or ectopic lesion)
- **MRI PITUITARY**—if suspect Cushing's disease
- **INFERIOR PETROSAL SINUS SAMPLING**—to differentiate pituitary vs. ectopic Cushing's
- **SERUM ACTH AFTER CRH STIMULATION**—ACTH would increase as pituitary tumors respond to CRH, but not in ectopic sources
- **OCTREOTIDE SCAN**—to localize ectopic ACTH producing tumors

DIAGNOSTIC ISSUES

INITIAL SCREENING TESTS—begin initial evaluation with 1 of 3 sensitive screening tests (i.e., 24 h urine cortisol, 1 mg overnight dexamethasone suppression test, or late night salivary cortisol). Follow-up abnormal test result with second test. If both results abnormal, proceed with confirmatory testing

1 MG OVERNIGHT DEXAMETHASONE SUPPRESSION TEST

- **PROTOCOL**
- **DAY 1**—baseline 8 AM serum cortisol and ACTH (optional). Give 1 mg dexamethasone between 11 PM and midnight
- **DAY 2**—measure 8 AM serum cortisol
- **INTERPRETATION**—8 AM serum cortisol <50 nmol/L following 1 mg of dexamethasone effectively rules out Cushing's. Failure to suppress requires further testing. Consult Endocrinology

TWO DAY ("2 MG") DEXAMETHASONE SUPPRESSION TEST—give dexamethasone 0.5 mg PO q6h for 2 days (e.g., 8 AM, 2 PM, 8 PM, 2 AM). Measure 8 AM cortisol level 6 h after last dose. Suppression of cortisol rules out Cushing's syndrome. Failure to suppress cortisol confirms Cushing's syndrome

TWO DAY ("8 MG") DEXAMETHASONE SUPPRESSION TEST—collect baseline 24 h urine cortisol, then give dexamethasone 2 mg PO q6h for 2 days (e.g., 8 AM, 2 PM, 8 PM, 2 AM) and continue urine collection for 48 h. Measure 8 AM cortisol 6 h after last dose. Partial suppression of cortisol (>50%) confirms pituitary Cushing's. Failure to suppress cortisol suggests ectopic or adrenal disease

MANAGEMENT

TREAT UNDERLYING CAUSE

- **IATROGENIC**—discontinue or reduce the dose of steroids if possible
- **PITUITARY**—first-line transsphenoidal surgery (90% cure rate) ± pituitary irradiation. Consider bilateral adrenalectomy and medical therapy (ketoconazole, pasireotide, metyrapone) for recurrent Cushing's disease
- **ADRENAL**—unilateral adrenalectomy
- **ECTOPIC**—resection of ectopic source if appropriate; otherwise, bilateral adrenalectomy and medical therapy (ketoconazole, pasireotide, metyrapone) may be considered

Related Topic
Lung Cancer (p. 203)

TREATMENT ISSUES

GLUCOCORTICOID REPLACEMENT—required in the post operative period. May take months to years for HPA axis to recover after transsphenoidal surgery or unilateral adrenalectomy. If bilateral adrenalectomy, lifelong replacement is needed. Do not forget stress dose!

SPECIFIC ENTITIES

PSEUDO-CUSHING'S SYNDROME

- **CAUSES**—hypercortisolism associated with severe stress, depression, obesity, alcoholism, pregnancy, and poorly-controlled diabetes
- **CLINICAL FEATURES**—may mimic Cushing's syndrome clinically, but rarely associated with dermatologic and muscular complications (e.g., bruising, thinning of skin, proximal muscle weakness)

EQUIVALENT DOSING TABLE

	Half-life (h)	Equivalent anti-inflammatory potency[a]	Equivalent mineralocorticoid potency[a]
Glucocorticoids			
Short acting			
Hydrocortisone	8–12	1	1
Cortisone	8–12	0.8	0.8
Intermediate acting			
Methylprednisolone	18–36	5	0.5
Prednisolone	18–36	4	0.8
Prednisone	18–36	4	0.8
Long acting			
Dexamethasone	36–54	30	0
Mineralocorticoid			
Fludrocortisone	12–24	12	125

[a]Relative to cortisol; higher number indicates greater potency

Hypocalcemia

DIFFERENTIAL DIAGNOSIS

PTH-RELATED (↓ **PTH**, ↑ **PO_4**)

- **HYPOPARATHYROIDISM**—surgery, irradiation, autoimmune, congenital, infiltrative, DiGeorge syndrome
- **FUNCTIONAL HYPOPARATHYROIDISM**—hypomagnesemia

PTH RESISTANCE (↑ **PTH**)—pseudohypoparathyroidism

NON-PTH-RELATED

- **VITAMIN D ABNORMALITIES (↑ PTH)**—vitamin D deficiency (nutritional, malabsorption), altered vitamin D metabolism (cirrhosis, chronic renal failure, anticonvulsants), vitamin D resistance
- **DRUGS**—phosphate infusion (hyperphosphatemia), calcitonin, bisphosphonates, plicamycin, loop diuretics
- **HUNGRY BONE SYNDROME**
- **ACUTE CAUSES**—acute pancreatitis, rhabdomyolysis, tumor lysis, large transfusions of citrate-containing blood products, toxic shock syndrome
- **OTHERS**—calcium malabsorption, hypoalbuminemia

PATHOPHYSIOLOGY

DEFINITION OF HYPOCALCEMIA—corrected serum Ca <2.1 mM [<8.4 mg/dL]. For every 10 mg/L [1 g/dL] ↓ in albumin, correct serum Ca by adding 0.2 mM [0.8 mg/dL]

PTH AND VITAMIN D

- **VITAMIN D FORMATION**—7-dehydrocholesterol → skin with UV → cholecalciferol (vitamin D_3 may be obtained via diet as well) → liver → 25OH D (used to determine vitamin D status) → kidney (stimulated by PTH or hypo-PO_4) → $1,25(OH)_2D_3$ (also known as calcitriol, the active form of vitamin D)
- **$1,25(OH)_2D_3$**—↑ Ca reabsorption at gut, kidney, and bone, ↑ PO_4 reabsorption at gut and kidney, ↓ PTH
- **PTH ACTION**—↑ Ca reabsorption at distal tubule and bone, ↓ PO_4 reabsorption at proximal tubule, ↑ $1,25(OH)_2D_3$

CLINICAL FEATURES

HISTORY—perioral paresthesias, tingling of fingers and toes, tetany, stridor (laryngospasm), seizures, confusion, weakness, past medical history (thyroid surgery), medications (loop diuretics, bisphosphonates, calcitonin, anticonvulsants)

CLINICAL FEATURES (CONT'D)

PHYSICAL—hypotension, Trousseau's sign, Chvostek's sign, carpal/pedal spasm, weakness

INVESTIGATIONS

BASIC

- **LABS**—Ca, albumin, Mg, PO_4, PTH, ALP, 25OH D, lytes, urea, creatinine

SPECIAL

- **ECG**—may show prolonged QT interval, ST changes

MANAGEMENT

SYMPTOM CONTROL—if severe symptoms, *Ca gluconate* 1–2 amps slow IV push then run a calcium drip 0.5–1.5 mg/kg/h, and *$MgSO_4$* 5 g IV over 4 h. If mild symptoms, *$CaCO_3$* 1–2 g PO TID–QID, *calcitriol* ($1,25(OH)_2D_3$) 0.25–0.5 µg daily–BID

TREAT UNDERLYING CAUSE

Related Topic
Hypophosphatemia (p. 94)

SPECIFIC ENTITIES

VITAMIN D DEFICIENCY

- **CAUSES**—vitamin D deficient diet and/or lack of exposure to sunlight, fat malabsorption syndromes, extensive burns (decreased skin conversion), nephrotic syndrome (renal loss), medications (anticonvulsants, glucocorticoids, immunosuppressants and HAART may lead to increased inactivation of $1,25(OH)_2D_3$), chronic kidney disease (decreased 1-OH activation), liver failure (decreased 25-OH activation)
- **CLINICAL FEATURES**—hypocalcemia, hypophosphatemia, osteomalacia with associated bone pain, osteoporosis with fractures and hyperparathyroidism. Vitamin D deficiency has also been postulated to be associated with chronic diseases such as cancer, cardiovascular diseases, diabetes, autoimmune disorders, and osteoarthritis
- **DIAGNOSIS**—25-hydroxyvitamin D is used to determine the level of vitamin D as it represents the combined level from both dietary and skin sources. A level <80 nmol/L is considered abnormal

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—treat underlying cause (e.g., malabsorption syndrome). For severe vitamin D deficiency (<25 nmol/L [<10 ng/mL]), *vitamin D3* 50,000 IU PO per week×6–8 weeks initially, then 50,000 IU PO q2–4 weeks×6–8 weeks, then reassess. For moderate deficiency (25–50 nmol/L [10–20 ng/mL]), *vitamin D3* 50,000 IU PO per week×6–8 weeks then 800–2,000 IU PO daily. For mild deficiency (50–75 nmol/L [20–30 ng/mL]), long-term use of *vitamin D3* 800–2,000 IU PO daily. For renal failure or hypoparathyroidism, *calcitriol* 0.25–1 µg PO BID should be given

Hypercalcemia

NEJM 2007 357:3

DIFFERENTIAL DIAGNOSIS

HYPERPARATHYROIDISM (most common cause among outpatients)—parathyroid adenoma, parathyroid hyperplasia, parathyroid carcinoma (rare)

MALIGNANCY (most common cause among inpatients)—lung, breast, prostate, renal, thyroid, GI, melanoma, sarcoma, multiple myeloma, lymphoma, leukemia

GRANULOMATOUS DISEASE—TB, sarcoidosis, lymphoma

ENDOCRINE—Addison's, hyperthyroidism, acromegaly

DRUGS—vitamin D toxicity, thiazide, lithium, tamoxifen

NUTRITIONAL—calcium supplement, vitamin D, vitamin A, milk alkali syndrome

OTHERS—familial hypocalciuric hypercalcemia (FHH), immobility, Zollinger–Ellison syndrome, acute renal failure

PATHOPHYSIOLOGY

DEFINITION OF HYPERCALCEMIA—corrected serum Ca >2.6 mmol/L [10.4 mg/dL]. For every 10 g/L (1 g/dL) ↓ in albumin, correct serum Ca by adding 0.2 mmol/L [0.8 mg/dL]

PTH ACTION—↑ Ca reabsorption at distal tubule and bone, ↓ PO_4 reabsorption at proximal tubule, ↑ $1,25(OH)_2D_3$

MALIGNANCY-RELATED MECHANISMS—local osteolytic bone lesions, humoral hypercalcemia of malignancy (PTH-related peptide, PTHrP), $1,25(OH)_2D_3$-secretion (lymphomas), ectopic hyperparathyroidism (very rare)

SARCOIDOSIS MECHANISM—unregulated synthesis of $1,25(OH)_2D_3$ from PTH-independent 1-hydroxylase activity in macrophages

CLINICAL FEATURES

SYMPTOMS

- **GI**—abdominal pain from constipation, pancreatitis, or peptic ulcer disease (moans), N&V

CLINICAL FEATURES (CONT'D)

- **MSK**—bony pain (groans)
- **RENAL**—calculi (stones), polyuria
- **CNS**—delirium (psychiatric overtones)

INVESTIGATIONS

BASIC

- **LABS**—Ca, albumin, ionized Ca (pH dependent), Mg, PO_4, PTH, ALP, 25OH D, $1,25(OH)_2D_3$, lytes, urea, creatinine

SPECIAL

- **MALIGNANCY WORKUP**—consider PTHrP, serum protein electrophoresis, urine protein electrophoresis, PSA, CEA, CA19–9, CA125, CA15–3, CXR
- **HYPERPARATHYROIDISM WORKUP**—consider US neck/thyroid and Tc-sestamibi parathyroid scan
- **FAMILIAL HYPOCALCIURIC HYPERCALCEMIA WORKUP**—24 h urine Ca and creatinine
- **MEN 2A WORKUP**—24 h urinary metanephrines
- **ECG**—bradycardia, heart block, ST changes, shortened QT interval

DIAGNOSTIC ISSUES

PTH LEVEL—↑ in hyperparathyroidism, ↑/N in familial hypocalciuric hypercalcemia, ↓ in vitamin D excess or PTHrP

DISTINGUISHING FEATURES BETWEEN IMPORTANT CAUSES OF HYPERCALCEMIA

	Primary PTH	Sarcoidosis	PTHrP	FHH
Ca	↑	↑	↑↑	↑
PO_4	↓	↑	↓/N	↓
PTH	↑↑/N	↓	↓	↑/N
PTHrP	–	–	↑	–
Calcitriol	↑	↑	↑	↓/N
Urine Ca	↑	↑/N	↑	↓

MANAGEMENT

SYMPTOM CONTROL—early rehydration, **NS** 200–500 mL/h IV ± ***furosemide*** 20–40 mg IV q8h PRN (use with caution and only when fully hydrated). If Ca ≥3.0 mmol/L [≥12 mg/dL], consider **bisphosphonates** (*pamidronate* 60–90 mg in 500 mL NS IV over 4 h or *zoledronate* 4 mg in 100 mL NS IV over 15 min). Malignancies may also respond to **steroids** (*prednisone* 60 mg PO daily × 10 days, *hydrocortisone* 200–500 mg IV daily), along with ***calcitonin*** 4–8 IU/kg SC q12h (note, intranasal calcitonin ineffective). Consider ***dialysis*** in patients with advanced renal failure where bisphosphonates are contraindicated and fluid challenge is difficult. Monitor urine output and renal function

TREAT UNDERLYING CAUSE

TREATMENT ISSUES

INDICATIONS FOR PARATHYROIDECTOMY FOR PRIMARY HYPERPARATHYROIDISM—age <50, symptomatic hypercalcemia (e.g., kidney stones [clinically or by imaging], neuromuscular disease), Ca >0.25 mmol/L [>1 mg/dL] above upper limit of normal, GFR <60 mL/min, osteoporosis with a *T* score of ≤ −2.5 at any site and/or previous fragility fracture, or inability to monitor medically

SPECIFIC ENTITIES

FAMILIAL HYPOCALCIURIC HYPERCALCEMIA (FHH)

- **PATHOPHYSIOLOGY**—autosomal dominant inactivating mutations in the calcium sensing receptor in parathyroid gland and kidneys, leading to a change in set point and increased serum calcium level to suppress PTH release and reabsorption of calcium in the kidneys
- **CLINICAL FEATURES**—usually asymptomatic. Renal stones uncommon
- **DIAGNOSIS**—↑ serum calcium, ↓ urinary calcium, ↑/N PTH. Family history can be helpful. Important to differentiate from primary hyperparathyroidism as 15–20% of FHH will have elevated PTH, and FHH does not respond to parathyroidectomy
- **TREATMENTS**—counseling and reassurance

MILK ALKALI SYNDROME

- **PATHOPHYSIOLOGY**—ingestion of significant amounts of calcium and absorbable alkali (e.g., $CaCO_3$) used as antacids and treatment of osteoporosis. The combination of increased alkali intake, decreased renal function, and hypercalcemia contributes to metabolic alkalosis, which decreases calcium excretion and in turn contributes to hypercalcemia
- **CLINICAL FEATURES**—triad of hypercalcemia, metabolic alkalosis, and renal insufficiency. May be acute or chronic (Burnett's syndrome) in presentation
- **DIAGNOSIS**—history of significant intake of calcium and absorbable alkali. ↑ serum calcium, N urinary calcium, ↓ PTH, and ↑/N PO_4
- **TREATMENTS**—low calcium diet. Hydration. Supportive measures

Osteoporosis

Canadian Osteoporosis Guidelines 2010
NEJM 1998 338:11 NEJM 2005 353:2

CAUSES

ENDOCRINE—estrogen deficiency (postmenopausal), hypogonadism (both female and male), hyperthyroidism, hyperparathyroidism
NUTRITION—decreased calcium/vitamin D intake, malabsorption syndromes (e.g., celiac disease), smoker, alcohol, caffeine intake
MEDICATIONS—glucocorticoids, heparin, cyclosporine, anticonvulsants (phenytoin, carbamazepine, barbiturates), methotrexate, LHRH agonists and antagonists, long-acting progestins, proton pump inhibitors

CAUSES (CONT'D)

OTHERS—age >50, liver disease (primary biliary cirrhosis), immobilization, small frame, decreased BMI <21 kg/m^2, Caucasian, Asian, Indo-Asian, family history

PATHOPHYSIOLOGY

DEFINITION—a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. WHO defines osteoporosis based on bone mineral

PATHOPHYSIOLOGY (CONT'D)

density (BMD) measurements, relative to a normal young adult population of the same sex and ethnicity. *T*-score is the number of standard deviations above/below the mean BMD compared to normal young adults, while *Z*-score compares with peers (of the same age, sex, and ethnicity)

Status	T-score
Normal	+2.5 to −1.0 (inclusive)
Osteopenia	Between −1.0 and −2.5
Osteoporosis	≤ −2.5
Severe osteoporosis	≤ −2.5 and fragility fracture

CLINICAL FEATURES

HISTORY—history of fragility fractures, height loss, Dowager's hump (thoracic kyphosis), milk/calcium consumption, sedentary lifestyle, past medical history, medications (steroids, heparin, cyclosporine, anticonvulsants), family history, smoking, alcohol, and caffeine intake

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS WOMAN HAVE OSTEOPOROSIS?

	LR+	LR−
History		
Self-reported humped back	3.0	0.85
Physical		
Weight <51 kg	7.3	0.8
BMI <25	4.5	0.5
Wall–occiput distance >0 cm (indicative of spinal fracture)	3.8	0.6
Rib–pelvis distance ≤2 finger breadths (indicative of spinal fracture)	3.8	0.6
Tooth count <20	3.4	0.8
Kyphosis	1.5	0.7
Decision Rules		
Simple calculated osteoporosis risk estimation (score ≥6)	1.2	0.02
Osteoporosis risk assessment instrument (score ≥9)	1.4	0.1
National osteoporosis foundation (score ≥1)	1.2	0.2
Age/body size/no estrogen (score ≥2)	1.6	0.3

APPROACH—"no single physical examination finding or combination of findings is sufficient to rule in osteoporosis or spinal fracture without further testing. Several convenient examination maneuvers including low body weight (<51 kg [<112 lb]), inability to place the back of the head against a wall when standing upright, low tooth count, self reported humped back, and rib-pelvis distance can significantly increase the likelihood of osteoporosis or spinal fracture and identify additional women who would benefit from earlier screening"

JAMA 2004 292:23

UPDATE—"BMI less than 25 in older women is the single best finding for detecting women with osteoporosis, performing better than decision rules. However, a BMI greater than 25 is not as informative as the decision rules for identifying women at the lowest risk of osteoporosis"

The Rational Clinical Examination. McGraw-Hill, 2009

INVESTIGATIONS

BASIC

- **LABS**—Ca, PO_4, albumin, 25OH D, PTH, ALP, CBC, creatinine, serum protein electrophoresis, TSH
- **IMAGING**—dual-energy X-ray absorptiometry (DEXA)

SPECIAL

- **IMAGING**—lateral thoracic and lumbar spine XR

DIAGNOSTIC AND PROGNOSTIC ISSUES

WHO SHOULD BE SCREENED WITH DEXA?

Older adults (≥50 years)

Age ≥65 years irrespective of risk factors

Risk factors for fracture *plus* age 50–64 years (♂) or menopausal (♀)

- Fragility fracture after age 40
- Prolonged glucocorticoid use (≥3 m cumulative exposure at prednisone-equivalent dose of ≥7.5 mg/day)
- Use of high-risk medication (e.g., androgen deprivation therapy, aromatase inhibitor)
- Parental hip fracture
- Current smoking
- High alcohol intake
- <60 kg body weight or major weight loss
- Height loss >10 cm
- Rheumatoid arthritis
- Presence of disorder strongly associated with osteoporosis (e.g., hypogonadism, malabsorption syndrome, primary hyperparathyroidism)

Younger adults (<50 years)

Fragility fracture (ever)

Prolonged glucocorticoid use (≥3 m cumulative exposure at prednisone-equivalent dose of ≥7.5 mg/day)

Use of high-risk medication (e.g., androgen deprivation therapy, aromatase inhibitor)

Hypogonadism or premature menopause (<45 years)

Malabsorption syndrome

Primary hyperparathyroidism

Presence of disorder strongly associated with rapid bone loss and/or fracture

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

FRACTURE RISK ASSESSMENT—estimate 10-year risk of a major osteoporotic fracture using a validated risk calculator such as the Fracture Risk Assessment tool (FRAX) of the World Health Organization, available online (country specific): www.sheffield.ac.uk/FRAX/tool.jsp?country=19

PROGNOSIS—an average 50-year-old Caucasian woman has a remaining lifetime risk of 40% of developing hip, vertebra, or wrist fracture

MANAGEMENT

LIFESTYLE CHANGES—calcium or vitamin D alone does not prevent hip fractures, but the combination of calcium and vitamin D appears to be beneficial. Recommend ***calcium*** through diet ± supplementation; advise *elemental calcium* 1000 mg/d if ♀ 19–50 years or ♂ 19–70 years; and *elemental calcium* 1200 mg/d if ♀ >50 years or ♂ >70 y. ***Vitamin D*** 800–2,000 IU PO daily. **Physical activity** >30 min 3×/week (weight bearing, core strengthening, and balance training). Consider **hip protectors** and **fall prevention strategies. Avoid excess caffeine** (>4 cups/day). **Smoking cessation**

MANAGEMENT (CONT'D)

MEDICATIONS—**bisphosphonates** (patients over the age of 50 should be stratified by their 10-year fracture risk. Patients who are at high risk [i.e., >20% risk of major osteoporotic fracture in the next 10 years, or prior history of fragility fracture] should be started on bisphosphonates. May also consider treating patients at moderate risk. Bisphosphonates should be taken with water >60 min before first meal, and remain upright × 30 min. *Alendronate* 70 mg PO weekly, *risedronate* 35 mg PO weekly, *zoledronic acid* 5 mg IV yearly). Duration of therapy is controversial (e.g., 5–10 years, followed by possible "drug holiday" vs. prolonged therapy in those at highest risk). **rhPTH** (*teriparatide*, stimulates bone formation and activates bone remodeling). **RANKL antibody** (*denosumab*, an anti-resorptive agent). **Calcitonin** (for analgesia, *calcitonin nasal spray* 200 IU intranasally daily, alternating nostrils). **Hormone replacement** (not for treatment of osteoporosis as primary indication, but sometimes used for treatment of menopausal vasomotor symptoms)

SPECIFIC ENTITIES

PAGET'S DISEASE OF BONE

- **PATHOPHYSIOLOGY**—focal, accelerated bone remodeling and metabolism disorder. Aggressive bone resorption by osteoclasts (skull, pelvis, vertebra, femur, tibia) that extends by 1 cm/year. This is followed by imperfect bone repair, leading to bone expansion and softening → pain, fracture, deformity, and rarely neoplastic transformation
- **CLINICAL FEATURES**—usually asymptomatic in early disease. Bone pain (achy, deep) and weakness develops later in the course, persists throughout the day and at rest, and may be worse at night. Bony deformity may lead to difficulties with weight bearing (femur, tibia), headaches and hearing loss (skull), and even neurological symptoms and paralysis (spine). More common in elderly
- **DIAGNOSIS**—↑ ALP is an excellent marker of disease extent and activity and can be used to follow treatment. Bone scan and plain X-rays can be diagnostic. In "mixed-stage" disease, cortical thickening (hyperostosis) disorganized coarse trabeculae (osteosclerosis), and bone expansion may be seen. In advanced ("burnt out") disease, bones are widened and heterogeneously ossified
- **TREATMENTS**—supportive care (NSAIDs, acetaminophen, opioids for pain). First-line therapy is **bisphosphonates** (*alendronate* 40 mg PO daily × 6 months, *risedronate* 30 mg PO daily × 2 months, or zoledronate 5 mg IV × 1 dose). Bisphosphonates can provide pain control, improve skeletal scintigraphy, and sometimes heal osteolytic lesions. Indications for therapy include symptoms related to active bone lesions (bone pain, headache, back pain, any other neurological syndromes, fissure fractures), prophylaxis in asymptomatic patients (weight-bearing bones involved and likely to progress), heart disease, and elective surgery planned for pagetic site (e.g., hip replacement) and hypercalcemia. If intolerant, consider ***calcitonin*** 50–100 U SC daily × 6–18 months (not as effective)

Hypertension NEJM 2006 355:6

See HYPERTENSION (p. 65)

Hyperlipidemia

See HYPERLIPIDEMIA (p. 70)

Amenorrhea

DIFFERENTIAL DIAGNOSIS

PRIMARY AMENORRHEA

- **HYPOTHALAMIC DYSFUNCTION**—functional, infiltrative (lymphoma, sarcoidosis), idiopathic hypogonadotropic hypogonadism (from congenital GnRH deficiency)
- **PITUITARY DYSFUNCTION**—prolactinoma, masses, craniopharyngioma, infiltrative
- **OVARIAN FAILURE**—Turner's syndrome (XO), gonadal agenesis/dysgenesis
- **OUTFLOW TRACT DISORDER**—imperforated hymen, transverse vaginal septum, isolated absence of cervix or vagina
- **OTHERS**—Mullerian agenesis, complete androgen insensitivity syndrome (XY), constitutional delay, causes of secondary amenorrhea

DIFFERENTIAL DIAGNOSIS (CONT'D)

SECONDARY AMENORRHEA

- **PREGNANCY**
- **THYROID DYSFUNCTION**—hyperthyroidism, hypothyroidism
- **ESTROGEN DEFICIENCY**—hypothalamic anovulation (functional, physical/emotional stress, strenuous exercise, weight loss, anorexia nervosa, chronic disease, CNS disease [infection, trauma, tumor], hyperprolactinemia, primary ovarian insufficiency, menopause
- **ANDROGEN EXCESS**—PCOS, ovarian tumors, adrenal tumors, Cushing's syndrome, nonclassic congenital adrenal hyperplasia, medications (testosterone, danazol)
- **ANATOMICAL ENDOMETRIAL DISORDERS**—adhesions (Asherman's syndrome), endometrial cancer, endometrial polyps, adenomyosis, leiomyomas

PATHOPHYSIOLOGY

DEFINITION OF AMENORRHEA

- **PRIMARY AMENORRHEA**—absence of menarche by age 15–16 years (in the presence of normal secondary sexual development), or absence of menarche by age 13–14 (without normal secondary sexual development). Note: absence of menarche after breast development always warrants investigation
- **SECONDARY AMENORRHEA**—absence of menses for >3 cycles or 6 months in a woman who previously had menses

CLINICAL FEATURES

HISTORY—characterize amenorrhea (onset, duration, previous menstruation), pregnancy and related symptoms, puberty milestones, headaches, visual field defects, fatigue, polyuria, polydipsia, weight change, physiologic or emotional stressors, galactorrhea, hot flashes, vaginal dryness, poor sleep, decreased libido, hirsutism, acne, past medical history (PCOS, obesity, hyperthyroidism, hypothyroidism, D&C), medications (birth control pills)

PHYSICAL—height and weight, vitals, visual fields, galactorrhea, Tanner staging (breasts, genitalia, pubic hair), pelvic examination. Also assess for hirsutism, acne, striae, acanthosis nigricans, vitiligo, and signs of hypothyroidism/hyperthyroidism. Perform pelvic examination

INVESTIGATIONS

BASIC

- **LABS**—prolactin, βhCG, FSH, LH, TSH, estradiol, testosterone, DHEAS, 17-OH progesterone
- **IMAGING**—US pelvis (if suspect ovarian tumor or uterine disorder), CT abd/pelvis (if suspect adrenal tumor)

SPECIAL

- **KARYOTYPE**
- **LAPAROSCOPY**
- **HYSTEROSALPINGOGRAM**—Asherman syndrome
- **PROGESTIN CHALLENGE TEST**—first rule-out pregnancy then administer progesterone for 7–10 days. If sufficient estrogen present, withdrawal bleeding will occur within a week, and suggests chronic anovulation (e.g., PCOS). Absence of withdrawal bleed suggests hypoestrogenism (e.g., ovarian failure), endometrial disease, or outflow tract obstruction

MANAGEMENT

TREAT UNDERLYING CAUSE—**hypothalamic suppression** (weight gain, treat illness). **Prolactinoma** (*bromocriptine* or *cabergoline*; see section on Pituitary Tumors p. 446 for details). **PCOS** (weight loss, birth control pill, progesterone, metformin if associated type 2 DM, IGT, adjunct for weight loss)

Hirsutism

DIFFERENTIAL DIAGNOSIS

TESTOSTERONE EXCESS

- **POLYCYSTIC OVARY SYNDROME**—most common, insulin resistance with hyperinsulinemia
- **IDIOPATHIC HIRSUTISM**—common
- **OVARIAN TUMORS**—Sertoli–Leydig cell tumor, granulosa-theca cell tumor
- **ADRENAL TUMORS**—carcinoma, adenoma
- **ANDROGEN THERAPY**—testosterone

DHEAS EXCESS

- **CONGENITAL ADRENAL HYPERPLASIA**
- **ADRENAL TUMORS**—carcinoma, adenoma
- **ANDROGEN THERAPY**—DHEA, danazol

PATHOPHYSIOLOGY

HIRSUTISM—androgen excess leading to excessive male pattern hair growth (terminal body hairs on face, chest, abdomen, and back). There may be associated acne and male-pattern balding

PATHOPHYSIOLOGY (CONT'D)

VIRILIZATION—significant androgen excess causing not only hirsutism but also deepening of voice, breast atrophy, increased muscle bulk, clitoromegaly, and increased libido

HYPERTRICHOSIS—excessive hair growth (soft, non-sexual areas) that is androgen independent. Most commonly familial or caused by systemic disorders (hypothyroidism, anorexia nervosa, malnutrition, porphyria, and dermatomyositis) or medications (phenytoin, penicillamine, diazoxide, minoxidil, or cyclosporine)

CLINICAL FEATURES

HISTORY—time course of symptoms, hirsutism and virilization symptoms, menstrual history, weight history, medications, family history

PHYSICAL—BMI, skin and hair growth pattern, signs of virilization, abdominal and pelvic examination

INVESTIGATIONS

BASIC

- **LABS**—testosterone, DHEAS, prolactin, LH, FSH, 17-OH progesterone, androstenedione
- **IMAGING**—US pelvis (if suspect ovarian tumor), CT abd/pelvis (if suspect adrenal tumor)

INVESTIGATIONS (CONT'D)

SPECIAL

- **LAPAROSCOPY/LAPAROTOMY**—if suspect ovarian tumor

DIAGNOSTIC ISSUES

DISTINGUISHING FEATURES

	PCOS	CAH	Idiopathic	Ovary tumor
Age	Puberty	Puberty/adulthood	Puberty	Adulthood
Menstruation	Altered	May be altered	Normal	Normal
Hirsutism	+	+	+	+++ virilization
Course	Slow	Slow	Slow	Acute
Testosterone/DHEAS	+	+	Normal	++
17-OH progesterone	–	+		

MANAGEMENT

TREAT UNDERLYING CAUSE—to eliminate excessive androgen production. Suppression of androgen only prevents new hair growth. After hyperandrogenism resolved, consider terminal hair removal (e.g., electrolysis)

SPECIFIC ENTITIES

POLYCYSTIC OVARIAN SYNDROME (PCOS)

- **PATHOPHYSIOLOGY**—increased androgen production in both puberty (increased ovarian steroid production) and adrenarche (increased adrenal androgen production). Increased insulin resistance leads to maturation arrest of the developing follicle. Increased testosterone is released from the ovaries instead. Cycles are anovulatory
- **CLINICAL FEATURES**—menstrual irregularity, hyperandrogenism (hirsutism, acne, male pattern balding), insulin resistance, elevated testosterone levels, LH/FSH >2 (insensitive; not necessary nor sufficient for diagnosis)
- **DIAGNOSIS**—2 out of 3 Rotterdam 2003 criteria: oligomenorrhea/anovulation, hyperandrogenism, and polycystic ovaries on US. Exclude other causes of menstrual irregularity/hyperandrogenism
- **TREATMENTS**—treat hirsutism (low-dose combination birth control pills, spironolactone, electrolysis, laser therapy), provide endometrial protection (low-dose combination birth control pills, progesterone), treat metabolic syndrome (diet, exercise, weight loss, metformin), and advise regarding fertility (clomiphene, metformin [ovulatory induction])

SPECIFIC ENTITIES (CONT'D)

IDIOPATHIC HIRSUTISM

- **CLINICAL FEATURES**—no menstrual irregularity, hirsutism
- **DIAGNOSIS**—normal androgen levels, diagnosis of exclusion
- **TREATMENTS**—hair removal (electrolysis, laser therapy), birth control pills, spironolactone

NON-CLASSIC CONGENITAL ADRENAL HYPERPLASIA

- **PATHOPHYSIOLOGY**—21-hydroxylase deficiency which leads to increased production of both 17-hydroxyprogesterone (the substrate for 21-hydroxylase and an androgen precursor) and androstenedione
- **CLINICAL FEATURES**—sometimes menstrual irregularity, hirsutism, no cortisol deficiency. May be indistinguishable from PCOS
- **DIAGNOSIS**—elevated 17-OH progesterone level
- **TREATMENTS**—highly individualized therapy. Treat hirsutism (birth control pills, spironolactone, electrolysis, laser therapy) and advise regarding fertility (low-dose glucocorticoid at hs to turn off ACTH stimulation to restore fertility)

12
DERMATOLOGY

Susan Chon

Eczema

DIFFERENTIAL DIAGNOSIS OF PRURITUS

INFLAMMATORY

- **DERMATITIS**—atopic dermatitis, asteatotic eczema, nummular eczema, dyshidrotic eczema, seborrheic dermatitis, stasis dermatitis, irritant contact dermatitis, allergic contact dermatitis, lichen simplex chronicus (neurodermatitis)
- **PSORIASIS**
- **PITYRIASIS LICHENOIDES**
- **URTICARIA**
- **DERMATITIS HERPETIFORMIS**
- **BULLOUS PEMPHIGOID**
- **GRAFT VS HOST DISEASE**

INFECTIONS—tinea, scabies, pediculosis corporis and pubis, pityriasis rosea

NEOPLASTIC—lymphoma (mycosis fungoides, Hodgkin lymphoma), myeloma, solid tumors, polycythemia vera

IATROGENIC

- **DRUG ERUPTION**—antibiotics, anti-epileptics
- **DRUG-INDUCED PRURITUS**—opiates, steroids, aspirin, antimalarials

SYSTEMIC

- **ENDOCRINE**—diabetes, hypothyroidism, hyperthyroidism
- **HEPATOBILIARY**—PBC, cholestasis
- **RENAL**—uremia, hemodialysis
- **NEUROLOGIC**—brachoradial pruritus, notalgia paresthetica, postherpetic neuralgia, multiple sclerosis, psychogenic itch
- **INFECTIONS**—HCV, HIV
- **OTHERS**—sarcoidosis, iron deficiency

PATHOPHYSIOLOGY

PATHOGENESIS—chronic inflammatory skin disorder characterized by dry skin and pruritus. Rubbing and scratching the skin promotes inflammation and leads to an itch–scratch cycle. It follows a relapsing course characterized by alternating periods of flares and remissions. Patients often have a personal or family history of eczema, asthma, or allergic rhinitis. Exacerbating factors may include cold weather, dust mites, pollens, infection, wool, pet fur, emotional stress, chemical irritants, and other allergens

CLINICAL FEATURES

FINDINGS—ill-defined pruritic erythematous plaques with excoriations. Neck and flexural prominence in adults and children. Pustules, honey-colored crusts, and weeping may be a sign of secondary infection

TYPES OF ECZEMA

- **ASTEATOTIC ECZEMA**—dry irritable skin in the elderly
- **NUMMULAR ECZEMA**—acral, coin-shaped patches of eczema usually on extremities
- **DYSHIDROTIC ECZEMA**—acute vesicular eczema of the palms and soles
- **XEROSIS/WINTER ITCH**—eczema secondary to dry conditions in winter

INVESTIGATIONS

SPECIAL (not typically performed)

- **LABS**—CBCD (eosinophilia) and IgE level (elevated)
- **BACTERIAL AND VIRAL CULTURES**—if there is a suspicion of a secondary infection

MANAGEMENT

TREATMENTS—**dry skin care** (unscented, hypoallergenic soaps, daily moisturizers). **Topical corticosteroids** BID × 3 weeks, off 1 week, repeat PRN (typically hydrocortisone 1–2.5% or desonide 0.05% for the face, triamcinolone 0.1% for the body), and topical calcineurin inhibitors (tacrolimus 0.1%, pimecrolimus 1%). **Antihistamines** (diphenhydramine, loratadine, fexofenadine, hydroxyzine, and doxepin).

D. Hui et al. (eds.), *Approach to Internal Medicine: A Resource Book for Clinical Practice*,
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MANAGEMENT (CONT'D)

Oral antibiotics × 7 days for superimposed *Staphylococcus aureus* infections (typically flucloxacillin or other penicillinase-resistant penicillin for MSSA and clindamycin, doxycycline or trimethoprim-sulfamethoxazole for MRSA)

SPECIFIC ENTITIES

DERMATITIS HERPETIFORMIS

- **ASSOCIATIONS**—Celiac disease, IgA nephropathy, autoimmune thyroid disease, autoimmune hepatitis, type 1 diabetes, SLE, Sjogren's syndrome, sarcoidosis, Addison's Disease, atrophic gastritis, vitiligo, and alopecia areata. Strong linkage to HLA-B8, DR3, and DQw2. Increased risk of non-Hodgkin's lymphoma
- **CLINICAL FEATURES**—pruritic papulovesicles on extensor surfaces and buttocks, rarely mucous membranes. Lesions tend to be symmetrically distributed
- **TREATMENTS**—dapsone and gluten-free diet. See Celiac disease (p. 139)

STASIS DERMATITIS

- **CLINICAL FEATURES**—erythematous pruritic and burning lesions found on lower limbs of older patients due to compromised venous or lymphatic return. With increased extravasation of blood into the surrounding tissues, the lesions become darker, scalier, and may even form stasis ulcers
- **TREATMENTS**—treat underlying cause. Leg elevation. Graduated compression stockings (after ankle–brachial index [ABI] checked). Topical steroids for acute exacerbations. Varicose veins may be treated with surgery, endovenous laser therapy or via sclerotherapy

SCABIES

- **CLINICAL FEATURES**—excoriations, eczematized and urticarial papules over trunk. Linear white burrows over finger webs, sides of hand, and flexural aspects of wrists. Confirmed by skin scrapings for mites and eggs
- **TREATMENTS**—first-line therapy with *permethrin* 5% cream × 1 dose, applied to the entire body from chin to soles, rinse off after 8–14 h. Second-line treatments include *ivermectin* 200 mcg/kg PO × 1 dose and repeat PO × 1 dose 2 weeks later, *lindane* 1% lotion or cream × 1 dose, rinse off after 8 h, and *benzyl benzoate* 10 or 25% lotions × 1 dose, rinse off after 24 h. Simultaneous treatment of patient and close contacts is recommended

NEJM 2006 354:16

Psoriasis Vulgaris

DIFFERENTIAL DIAGNOSIS OF PAPULOSQUAMOUS LESIONS

INFLAMMATORY—psoriasis vulgaris, lichen planus, nummular eczema, discoid lupus
INFECTIONS—tinea, pityriasis rosea, secondary syphilis, seborrheic dermatitis
MALIGNANCY—mycosis fungoides, basal cell carcinoma (BCC), squamous cell carcinoma (SCC)
IATROGENIC—drug eruption

PATHOPHYSIOLOGY

INFLAMMATION—a chronic inflammatory skin disorder with a polygenic predisposition and sometimes an environmental triggering factor (trauma/Koebner phenomenon, infections, drugs, alcohol ingestion, emotional stress)

CLINICAL FEATURES

FINDINGS—well-circumscribed, bright salmon red color, silvery micaceous scaly plaques. Predilection for the scalp and extensor regions. Nails may show pitting changes, "oil spots", onycholysis, and subungual debris which may be helpful in making the diagnosis. All patients regardless of skin severity should be screened for inflammatory arthritis that is worse in the mornings, associated with joint stiffness and swelling ± dactylitis. Consider screening for hyperlipidemia, coronary artery disease, and diabetes in patients with risk factors as there is an increased predilection in patients with psoriasis

SUBTYPES

- **CHRONIC PLAQUE PSORIASIS**—predilection for scalp, elbows, and knees. Symmetric, sharply demarcated erythematous plaques with silvery

CLINICAL FEATURES (CONT'D)

scales that when scratched off reveals punctate blood droplets (Auspitz sign)

- **GUTTATE PSORIASIS**—predilection for trunk. May follow a streptococcal infection. Multiple discrete erythematous papules with silvery scales
- **PALMOPLANTAR PSORIASIS**—mild to severe forms. Well-demarcated erythematous plaque with silver scales. Cracking, fissures, or bleeding may be seen. Pustular variant also found
- **INVERSE PSORIASIS**—perianal, genital, and axillary well-demarcated erythematous plaques that are more likely to be macerated and fissured due to location in a moist and warm environment
- **ERYTHRODERMIC PSORIASIS**—generalized erythema ± characteristic erythematous plaques with white-silver scale and nail changes. Often spares the face
- **PUSTULAR PSORIASIS**—initial stinging and burning in area may promote scratching, followed by eruption of sterile pustules

INVESTIGATIONS

SPECIAL (not typically performed)

- **MICROBIOLOGY**—throat C&S (if guttate psoriasis)
- **KOH PREPARATION**—if suspect tinea
- **SKIN BIOPSY**

MANAGEMENT

TREAT UNDERLYING CAUSE—**topical therapy** with corticosteroids (triamcinolone/fluocinolone, fluocinonide, betamethasone dipropionate and clobetasol) and vitamin D analogs. Topical calcineurin inhibitors may be used on the face and intertriginous areas. If unable to control, **light therapy** with either UVB or PUVA may be considered, but requires 2–3 visits/week for months. Traditional **systemic therapies** including acitretin, cyclosporine, and methotrexate should be considered in patients with moderate to severe psoriasis with >10% body surface involvement or severe functional impairment (hands, feet, arthritis, and genitals). If unresponsive or unable to tolerate these, **biologic therapy** such as the **TNFα inhibitors** (infliximab, adalimumab, golimumab, etanercept) or ustekinumab (anti-IL 12/23) should be considered for psoriatic arthritis. Avoid systemic steroids as discontinuation may cause generalized pustular psoriasis

SPECIFIC ENTITIES

PITYRIASIS ROSEA

- **PATHOPHYSIOLOGY**—human herpesvirus-6/7 may be the etiologic agent, although this disorder does not seem to be contagious
- **CLINICAL FEATURES**—herald plaque (2–5 cm, round, redder, scaly) followed by many smaller plaques. Resolves spontaneously after 2–5 weeks
- **TREATMENTS**—no treatment needed usually. Topical steroid to relieve pruritus

LICHEN PLANUS

- **PATHOPHYSIOLOGY**—autoimmune disease with lymphocytic infiltration in epidermis
- **ASSOCIATIONS**—drugs (β-blockers, methyldopa, penicillamine, NSAIDs, ACE inhibitors, carbamazepine, gold, lithium), HCV infection
- **CLINICAL FEATURES ★5 P's★**—**P**urple, **P**ruritic, **P**olygonal, **P**lanar (flat-topped) **P**apules. May also see fine white lines on the surface (Wickham's striae). Commonly seen in flexor wrists, forearms, and buccal mucosal (lacy white reticular lesions). Lesions may last for a year
- **TREATMENTS**—no treatment needed usually. Topical steroids, antihistamines, and anti-inflammatories to relieve pruritus. Investigate for associated causes

SEBORRHEIC DERMATITIS

- **PATHOPHYSIOLOGY**—a common skin disorder affecting areas rich in sebaceous glands such as the scalp, face, mid-chest, and intertriginous areas. It is caused by the yeast *Malassezia furfur* (formerly known as *Pityrosporum ovale*), *M. restricta*, and *M. globosa,* with increased host response leading to dermatitis. It is also known as "dandruff" in adults
- **CLINICAL FEATURES**—pink to erythematous plaques with yellow scales or greasy crusts, which may occasionally be pruritic
- **TREATMENTS**—gentle emollients, ketoconazole shampoo or cream, and 1–2.5% hydrocortisone cream. Severe scalp involvement in an adult may also be treated with shampoos containing selenium sulfide, zinc pyrithione, and stronger steroid liquids

Related Topic
Psoriatic Arthritis (p. 320)

SPECIFIC ENTITIES (CONT'D)

URTICARIA (HIVES)

- **PATHOPHYSIOLOGY**—an acute (<6 weeks) or chronic (>6 weeks) type I hypersensitivity reaction. Most cases are idiopathic but triggers may include infections and medications
- **CLINICAL FEATURES**—characterized by superficial transient edema with pink highly pruritic papules or plaques with individual lesions having rapid onset and resolution within 24 h. Dermatographism is common where wheals may be induced after stroking the skin
- **TREATMENTS**—non-sedating antihistamines during the day and scheduled sedating antihistamines at night. Systemic glucocorticoids may be used when severe, but courses should be tapered over 5–7 days

DERMATOPHYTE (TINEA) INFECTIONS

- **PATHOPHYSIOLOGY**—*Trichophyton*, *Epidermophyton*, *Microsporum* are fungi that can uniquely dissolve keratin
- **CLINICAL FEATURES**—asymptomatic, scaling erythematous patches/plaques that slowly enlarge over scalp (tinea capitis), feet (tinea pedis), hand (tinea manuum), groin (tinea cruris), body (tinea corporis), and nails (onychomycosis). May be associated with pruritus and vesicles

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—skin and nail lesions may be difficult to distinguish from psoriasis, eczematous conditions, and lichen planus. KOH examination from skin scrapings shows segmented hyphae and spores
- **TREATMENTS**—**tinea capitis** (*griseofulvin* 20–25 mg/kg/day for 6–8 weeks, terbinafine, itraconazole), **tinea pedis or cruris** (*terbinafine* 1% cream daily-BID, clotrimazole/Lotrimin 1% cream BID), **onychomycosis** (*terbinafine* 250 mg PO daily × 6–12 weeks, *itraconazole* 200 mg PO daily × 8–12 weeks. Need to monitor liver enzymes)

TINEA VERSICOLOR

- **PATHOPHYSIOLOGY**—Malassezia furfur
- **CLINICAL FEATURES**—young adult with hypopigmented, light brown, or salmon-colored scaly macules coalescing into patches
- **DIAGNOSIS**—KOH examination from skin scrapings show classic "spaghetti and meatballs" pattern representing hyphae and spores
- **TREATMENTS**—**topical** (*terbinafine* 1% cream daily BID, *clotrimazole* 1% cream BID, selenium sulfide 2.5% shampoo or lotion), **systemic** (ketoconazole, fluconazole, itraconazole)

GROIN SKIN LESIONS—common causes include tinea cruris, candidiasis, erythrasma (*Corynebacterium minutissimum*), and inverse psoriasis

Acne Vulgaris

NEJM 2005 352:14

DIFFERENTIAL DIAGNOSIS OF ACNEIFORM LESIONS

ACNE VULGARIS
ROSACEA
PERIORAL DERMATITIS
DRUGS—**EGFR inhibitors** (erlotinib, gefitinib, cetuximab, panitumumab) and **oral corticosteroids** (prednisone, dexamethasone) can cause pustular folliculitis

PATHOPHYSIOLOGY

PATHOGENESIS—condition affecting pilosebaceous units, commonly seen during puberty. Pathogenesis involves androgens, follicular keratinization, and the Gram-positive bacteria *Proprionibacterium acnes*. Lesions may present as non-inflammatory comedones or inflammatory papules. Inflammatory cysts may leave behind hyperpigmentation and sometimes scaring

PATHOPHYSIOLOGY (CONT'D)

RISK FACTORS—**drugs** (steroids, phenytoin, lithium), **androgen excess** (PCOS, Cushing's, congenital adrenal hyperplasia)

CLINICAL FEATURES

SEVERITY OF ACNE VULGARIS

- **MILD**—mainly comedones with few papules/pustules
- **MODERATE**—moderate papules and pustules (10–40) and comedones (10–40)
- **MODERATELY SEVERE**—numerous papules and pustules (40–100) and many comedones (40–100). May have nodular inflamed lesions (up to 5). Widespread involvement of face, chest and back
- **SEVERE**—nodulocystic acne and acne conglobata with many nodular or pustular lesions

TYPICAL PRESENTATION—teenager with open comedones (blackheads), closed comedones

CLINICAL FEATURES (CONT'D)

(white heads), erythematous papules, pustules, cysts and scarring over face, shoulders, upper chest, and back

INVESTIGATIONS

SPECIAL (not typically performed)

- **ENDOCRINE WORKUP**—testosterone, 24-h urinary cortisol

MANAGEMENT

TREAT UNDERLYING CAUSE

- **FIRST-LINE AGENTS**—topical agents include benzoyl peroxide 2.5–10% daily-BID, sulfur-based washes, topical retinoids (*tretinoin* 0.025–0.1% qhs, *tazarotene* qhs), and topical antibiotics (*clindamycin* daily-BID, *erythromycin* daily-BID)
- **MODERATE CASES**—oral antibiotic (*minocycline* 50–100 mg daily-BID, *doxycycline* 50–100 mg daily-BID, *trimethoprim–sulfamethoxazole* 160/800 BID, *tetracycline* 250–500 mg daily-BID, *erythromycin* 250–500 mg BID–QID) or antiandrogen therapy such as birth control pills may be used in female patients
- **SEVERE CASES**—respond well to oral *isotretinoin* 0.5–1 mg/kg/day, with a cumulative dose of 120 mg/day. Close monitoring with laboratory and clinical follow-up. High risk for teratogenicity

TREATMENT ISSUES

RETINOIDS—inhibit sebum excretion and *P. acnes*. Reserved for severe nodulocystic acne. Topical retinoids may cause photosensitivity. Retinoids should never be used in pregnant women as highly teratogenic. Fertile women should take oral contraceptive pills 2 months before treatment continuing until 1 month after discontinuing oral retinoids

SPECIFIC ENTITIES

ROSACEA

- **CLINICAL FEATURES**—middle age adults with central facial telangiectasias, flushing (especially after ingestion of hot liquids, alcohol, spicy foods, and other triggers), and acneiform papulopustules in cheeks, nose, forehead, and chin. No comedones. Maybe associated with rhinophyma (more in men), conjunctivitis, iritis, and keratitis
- **TREATMENTS**—oral antibiotics (tetracycline, erythromycin), topical antibiotics (metronidazole 0.75%), sulfur-based products (sodium sulfaceta mid lotion 10%), pulsed dye laser

PERIORAL DERMATITIS

- **CLINICAL FEATURES**—young woman with papules and pustules over chin, upper lip, and nasal labial folds
- **TREATMENTS**—oral antibiotics (tetracycline, erythromycin)

Exanthematous Lesions

DIFFERENTIAL DIAGNOSIS OF EXANTHEMATOUS LESIONS

INFECTIONS

- **VIRAL**—HCV, HIV, EBV, parvovirus B19, measles, rubella, roseola
- **BACTERIAL**—toxic shock, Staphylococcal scalded skin syndrome, Streptococcal toxic shock syndrome, scarlet fever, meningococcus, Rocky Mountain spotted fever, typhus

IATROGENIC—medications (see DRUG ERUPTIONS p. 422)

CLINICAL FEATURES

TYPICAL PRESENTATION—widespread erythematous maculopapular lesions that may be accompanied by fever and malaise

MANAGEMENT

TREAT UNDERLYING CAUSE—discontinue any offending drugs. Usually resolve spontaneously

Related Topic
Fever and Rash (p. 260)

SPECIFIC ENTITIES

PARVOVIRUS B19—slapped cheek rash on face and erythematous eruption on trunk, neck, and extremities. Also called fifth disease or erythema infectiosum. Fever may be present. Parvovirus B19 is also associated with aplastic anemia, polyarthritis, and fetal hydrops

SPECIFIC ENTITIES (CONT'D)

STAPHYLOCOCCAL SCALDED SKIN SYNDROME (SSSS)

- **PATHOPHYSIOLOGY**—exfoliatins produced by specific strains of staphylococci leading to desquamative disorder with cleavage at the granular layer of the dermis and acute epidermolysis
- **CLINICAL FEATURES**—fever, malaise, generalized macular erythematous rash that evolves rapidly into a scarlatiniform (sandpaper-like) rash, followed by an exfoliative phase with perioral exudation and crusting. Large radial fissures "sunburst" around the mouth and are one of the diagnostic features. Nikolsky sign positive. Increased risk in children/infants, renal failure, immunocompromised
- **DIAGNOSIS**—culture from a site other than the blisters (blood, conjunctivae, nasopharynx) demonstrating staphylococci
- **TREATMENTS**—hospitalization and IV antibiotics for treatment of Staphylococci (nafcillin/oxacillin first line, vancomycin if failing therapy or high prevalence or risk of MRSA)

TOXIC SHOCK SYNDROME

- **PATHOPHYSIOLOGY**—exotoxin by specific strains of *S. aureus* or group A *Streptococcus* (toxic shock syndrome toxin-1 TSST-1) acting as superantigens, activating T cells, leading to cleavage at the granular layer of the dermis

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—young person with fever, malaise, generalized macular, erythematous rash including mucous membranes, palms and soles, evolves into petechiae, vesicles, and bullae. Ulcerations may be seen on mucous membranes. Exclude retained foreign bodies (especially tampons, contraceptive sponges). Hypotension and organ failure may occur
- **TREATMENTS**—fluid resuscitation as needed, *vancomycin* (30 mg/kg/day IV divided BID) or β-lactam plus *clindamycin* (900 mg IV q8h). If unresponsive to fluids or vasopressors, consider *IVIG* (400 mg/kg × 1 dose, limited evidence)

SCARLET FEVER

- **PATHOPHYSIOLOGY**—erythrogenic toxin by specific strains of group A *Streptococcus* leading to cleavage at the granular layer of the dermis
- **CLINICAL FEATURES**—children with fever, sore throat, petechiae, and punctate red macules on hard and soft palate and uvula (Forchheimer spots), circumoral pallor, strawberry tongue, erythematous patches involving ears and chest, extend to trunk and extremities and accentuate in skin folds (Pastia lines). Evolves to sandpaper-like appearance. Desquamation happens 7–10 days after resolution of rash
- **TREATMENTS**—antibiotics and fluid resuscitation as needed

Stevens–Johnson Syndrome/Toxic Epidermal Necrolysis

DIFFERENTIAL DIAGNOSIS OF VESICLES/BULLOUS LESIONS

INFLAMMATORY—bullous pemphigoid*, pemphigus vulgaris*, porphyria cutanea tarda*, lupus*, dermatitis herpetiformis, erythema multiforme, contact dermatitis

INFECTIONS

- **BACTERIAL**—bullous impetigo*, Staphylococcal scalded skin syndrome, toxic shock syndrome
- **VIRAL**—HSV, VZV, molluscum contagiosum, Coxsackie virus

NEOPLASTIC—paraneoplastic pemphigus

IATROGENIC—Stevens–Johnson syndrome*, toxic epidermal necrolysis*

*bullous lesions may be seen with or without vesicles

PATHOPHYSIOLOGY

HYPERSENSITIVITY REACTION—Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) lie on a spectrum of serious, life-threatening illness characterized by extensive epidermal necrosis. By definition, SJS involves less than 10% of the body surface area (BSA) and TEN involves greater than 30% of the BSA. Involvement of 10–30% BSA is an overlap between the two. Drugs are the most common offending agents, but *Mycoplasma pneumoniae*, viruses, various chemicals and immunizations have also been associated with SJS/TEN

COMMONLY ASSOCIATED DRUGS ★4A'S★

- **A**llopurinol
- **A**ntibiotics—sulfamethoxazole, cephalosporins, penicillins, quinolones, macrolides
- **A**nti-inflammatory drugs—NSAIDs, salicylates

PATHOPHYSIOLOGY (CONT'D)

- **A**nticonvulsants—carbamazepine, phenytoin, lamotrigine, phenobarbital

CLINICAL FEATURES

TYPICAL PRESENTATION—patients usually develop symptoms within 2–3 weeks after drug exposure, more rapidly in previously exposed patients. The prodrome involves a flu-like syndrome with fever, malaise, arthralgias, myalgias, and mucous membrane lesions. This is followed by the development of irregular targetlike lesions often with necrotic centers that coalesce over time. Flaccid blisters form that spread with pressure (Nikolsky sign) resulting in sheet-like loss of epidermis and exposure of the underlying dermis. Ninety percent of patients have mucous membrane involvement and 60% have ocular involvement

NIKOLSKY'S SIGN—pressing on the edges of an intact blister helps to discriminate between an intraepidermal blistering process (pemphigoid vulgaris, blister extends and breaks easily) and a subepidermal process (TEN, bullous pemphigoid, blister would not advance)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, Cr, urea
- **MICROBIOLOGY**—fluid C&S, HSV serology, VZV serology
- **SKIN BIOPSY**

PROGNOSTIC ISSUES

PROGNOSIS—mortality rate for SJS and TEN is about 5 and 30–50%, respectively, typically from sepsis and multi-organ failure

MANAGEMENT

TREAT UNDERLYING CAUSE—identifying and stopping the offending drug. Supportive measures (wound and ocular care, adequate fluid replacement, prevention of infection and vulvovaginal complications). Corticosteroids may be helpful but can be deleterious in severe forms of SJS/TEN. High-dose IVIG is controversial but may halt progression. Systemic antibiotics may be necessary

SUPPORTIVE MEASURES—patients should be managed in a burn unit or ICU, as electrolyte abnormalities, renal failure, and pulmonary edema may occur

SPECIFIC ENTITIES

ERYTHEMA MULTIFORME

- **PATHOPHYSIOLOGY**—immune-mediated hypersensitivity reaction involving the skin and VERY LIMITED mucous membranes
- **ASSOCIATIONS**—infections (HSV, HBV, HCV, mycoplasma, bacterial, fungal), drugs, pregnancy, malignancy
- **CLINICAL FEATURES**—skin lesions usually preceded by a few weeks of viral prodrome. Macules or papules evolve to form targetoid lesions. Palms, soles, forearms, legs most commonly affected
- **TREATMENTS**—discontinue offending drugs. Treat suspected HSV infection with appropriate antivirals

IMPETIGO

- **PATHOPHYSIOLOGY**—intra-epidermal infection by *Staphylococcus aureus* or β-hemolytic streptococci
- **CLINICAL FEATURES**—in bullous form, flaccid, pus-filled lesions often found in intertriginous areas. More commonly found in children
- **TREATMENTS**—antibiotics (cefazolin, cephalexin)

BULLOUS PEMPHIGOID

- **PATHOPHYSIOLOGY**—autoimmune disease with IgG binding to subepidermal proteins (BP antigen 180 or 230), leading to separation of epidermis from dermis
- **ASSOCIATIONS**—furosemide, captopril, thiazide, spironolactone, penicillamine, phenothiazines, tricyclic antidepressants, benzodiazepines
- **CLINICAL FEATURES**—multiple chronic, pruritic, tense blisters in the elderly. Commonly affecting flexural areas, axillae, and groin. Mucous membranes affected in <1/3 of cases, but rarely presenting feature. Nikolsky's sign negative
- **TREATMENTS**—discontinue offending drugs. Treat with anti-inflammatories and immunosuppressants, including tetracycline and niacinamide. *Prednisone* 1–2 mg/kg PO daily. Methotrexate, azathioprine and mycophenolate mofetil. In mild or localized disease, treat with Class I topical steroids (clobetasol propionate)

PEMPHIGUS VULGARIS

- **PATHOPHYSIOLOGY**—autoimmune disease with IgG binding to intraepidermal proteins (Desmoglein 1 and 3), leading to separation of keratinocytes in epidermis

SPECIFIC ENTITIES (CONT'D)

- **ASSOCIATIONS**—penicillamine, captopril, enalapril, penicillins, cephalosporins, malignancies (paraneoplastic)
- **CLINICAL FEATURES**—acute onset of multiple flaccid blisters. Mucous membranes usually affected first, with spread to scalp, face, chest, and groin. Nikolsky's sign positive. Lesions prone to rupture and infections. May be life-threatening. May be paraneoplastic
- **TREATMENTS**—discontinue offending drugs. Consider burn unit admission, supportive fluids. *Prednisone* 1–2 mg/kg PO daily. Azathioprine, cyclosporine, mycophenolate mofetil, rituximab, plasmapheresis, IVIG

SPECIFIC ENTITIES (CONT'D)

HERPES SIMPLEX VIRUS (HSV) 1 OR 2

- **CLINICAL FEATURES**—vesicles followed by ulcers in oral (gingivostomatitis) or genital areas
- **DIAGNOSIS**—scraping of vesicle stained with Wright–Giemsa stain shows acantholytic ballooned and multi-nucleated cells
- **TREATMENTS**—acyclovir, valacyclovir, famciclovir

VARICELLA ZOSTER VIRUS (VZV)

- **CLINICAL FEATURES**—crops of vesicles over entire body (varicella) or specific dermatome with reactivation (zoster, also known as shingles)
- **TREATMENTS**—acyclovir, valacyclovir, famciclovir. Amitriptyline, gabapentin, and opioids may be useful for post-herpetic neuralgia. Zoster vaccination for older adults (>50-60 years)

Ulcers

DIFFERENTIAL DIAGNOSIS OF ULCERS

VENOUS HYPERTENSION

- **STASIS**—immobility, CHF, incompetent valves, pregnancy
- **DVT**

ATHEROSCLEROTIC

NEUROPATHIC—diabetes, leprosy, syphilis, syringomyelia, peripheral neuropathy

VASCULITIC—temporal arteritis, polyarteritis nodosa, systemic sclerosis

INFECTIONS

- **BACTERIAL**—gumma, mycobacteria
- **VIRAL**—chronic ulcerative herpes simplex
- **FUNGAL**—deep fungal infections
- **PARASITIC**—cutaneous leishmaniasis, cutaneous amebiasis

TUMOR—squamous cell carcinoma, basal cell carcinoma, melanoma, Kaposi's sarcoma

TRAUMA

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, glucose, urea, Cr, HbA1C
- **MICROBIOLOGY**—wound Gram stain, AFB, C&S, TB culture
- **ANKLE BRACHIAL INDEX**—<0.8 indicates arterial origin
- **IMAGING**—doppler ultrasound, venous plethysmography

INVESTIGATIONS (CONT'D)

SPECIAL

- **PYODERMA GANGRENOSUM**
  - **COLONOSCOPY**—if suspect IBD
  - **MALIGNANCY WORKUP**—serum protein electrophoresis, CXR
  - **INFLAMMATORY WORKUP**—ESR, antiphospholipid antibody, antineutrophil cytoplasmic antibodies, cryoglobulins
  - **SKIN BIOPSY**—mainly to rule out possible skin malignancies in the ulcer and to exclude other diagnoses. Include inflamed border for histologic evaluation and ulcer edge for bacterial, fungal, and mycobacterial culture

MANAGEMENT

See SPECIFIC ENTITIES for details

SPECIFIC ENTITIES

VENOUS ULCERS

- **PATHOPHYSIOLOGY**—result from chronic increases in venous pressure due to either incompetent valves, failure of pump activity from immobility or obesity, or venous outflow obstruction. Increased pressure in the venous system results in dilatation of the capillary beds and chronic inflammation that breaks down the extracellular matrix

SPECIFIC ENTITIES (CONT'D)

- **RISK FACTORS**—obesity, HF, history of DVT and/or thrombophlebitis, varicose veins, prolonged standing, and multiple pregnancies
- **CLINICAL FEATURES**—shallow, relatively painless, and typically located from the mid-calf to the ankle, classically on the medial malleolus. Other common lower extremity findings include edema, lipodermatosclerosis (firm and indurated skin), hyperpigmentation, and dermatitis
- **TREATMENTS**—compression stockings (need to rule out arterial insufficiency), leg elevation, walking/physiotherapy. Occlusive dressing (DuoDerm; weekly if not infected vs. twice daily if infected). Diuretics (decrease leg edema). Antibiotics if super-infected. Superficial vein surgery may prevent recurrence in some patients

ATHEROSCLEROTIC ULCERS

- **PATHOPHYSIOLOGY**—result from peripheral artery disease or vasculitis that prevents adequate blood flow to the lower extremity. Inadequate oxygen and nutrient delivery results in tissue breakdown and arterial necrosis
- **RISK FACTORS**—atherosclerosis, peripheral artery disease, diabetes mellitus, obesity, smoking, rheumatic disease, Buerger's disease, hemoglobinopathies
- **CLINICAL FEATURES**—ulcers tend to be well defined and appear "punched out" with a gray or black necrotic base. Lesions occur over distal sites such as toes and bony prominences and are very painful. Associated features include intermittent claudication, diminished peripheral pulses, and prolonged capillary refill
- **TREATMENTS**—treat underlying cause, such as surgical bypass for peripheral arterial disease. Avoidance of trauma. Apply moist occlusive dressings. Surgical debridement and systemic antibiotics may be necessary if infected. See PERIPHERAL VASCULAR DISEASE (p. 62)

NEUROPATHIC ULCERS

- **PATHOPHYSIOLOGY**—most common in diabetic patients. A combination of sensory and motor neuropathy due to enzymatic glycosylation impairs protective sensation and alters the distribution of forces on the lower extremity during normal movement. Many diabetic patients have a combination of neuropathic and arterial ulcers

SPECIFIC ENTITIES (CONT'D)

- **RISK FACTORS**—diabetes mellitus, syphilis, leprosy, and peripheral neuropathies
- **CLINICAL FEATURES**—a pure neuropathic ulcer is painless. There is diminished sensation in the lower extremity. Patients have warm extremities with palpable pulses, as opposed to arterial ulcers
- **TREATMENTS**—diabetic patients require tight glucose control. Treat infection with systemic antibiotics. Debridement of the ulcer, hyperbaric oxygen therapy, and occlusive dressings are applied to promote wound healing. Immobilization and orthotic devices are used to alleviate pressure on the wound. Amputation may be required in severe cases

PYODERMA GANGRENOSUM

- **PATHOPHYSIOLOGY**—chronic condition that involves neutrophilic destruction of tissue
- **RISK FACTORS**—approximately 50% of patients have an underlying systemic illness, including ulcerative colitis (most common), Crohn's disease, rheumatoid arthritis, lymphoproliferative disorder (lymphoma, leukemia, MDS), Behçet's disease, and active hepatitis
- **CLINICAL FEATURES**—initially, lesions appear as small, painful, erythematous papules that spread concentrically, evolving into pustules. Tissue breakdown and ulceration occur rapidly. Ulcers classically have dusky-red, violaceous, irregular borders with a purulent exudate and undermining. Lesions are typically solitary, but may be multiple and coalesce into larger ulcers. It is typically found on the lower extremity, but other common sites include the buttocks, abdomen, and face. Exhibits pathergy, often arising in sites of injury (surgical incision, needle prick, insect bite). ESR may be elevated. Classically worsens with attempted biopsy or debridement
- **TREATMENTS**—treat underlying causes where possible. Immunosuppressive and immunomodulator therapy such as high dose oral or IV glucocorticoids (*prednisone* 60–80 mg PO daily, *pulse methylprednisolone* 1 g IV daily × 3 day), cyclosporine, and TNF *α* blockade (infliximab) and *IVIG* 400 mg/kg IV daily × 5 day or 1 g/kg IV daily × 2 day have been effective. Other options include sulfasalazine, sulfones, minocycline, and dapsone. Topical and intralesional steroids and tacrolimus have also been used

Melanoma and Skin Tumors

NEJM 2005 353:21; NEJM 2004 351:10; NEJM 2001 344:13

DIFFERENTIAL DIAGNOSIS OF PIGMENTED LESIONS

BENIGN—nevus (congenital, acquired), freckle, seborrheic keratosis, café-au-Lait
PRE-MALIGNANT—dysplastic nevi syndrome
MALIGNANT—melanoma (superficial spreading, nodular, lentigo maligna, acral lentiginous), **pigmented basal cell carcinoma**

PATHOPHYSIOLOGY

RISK FACTORS OF MELANOMA

- **GENETICS**—fair skin/ethnicity, red/blonde hair, blue eyes, family history
- **NEVI**—number of common/atypical nevi (marker of sun exposure), familial dysplastic nevus syndrome, previous melanoma
- **EXPOSURE**—intermittent intense sun exposure, phototherapy, immunosuppression

HISTOLOGIC TYPE

- **SUPERFICIAL SPREADING** (70%)—fifth decade of life, both sexes, initial radial growth, common on back, posterior legs of women
- **NODULAR** (15%)—grows rapidly vertically. More common in men
- **LENTIGO MALIGNA** (10–15%)—sun-damaged skin, older patients, 5–20-year radial growth phase
- **ACRAL LENTIGINOUS**—most common melanoma in pigmented patients. Affects palms, soles, and nails

CLINICAL FEATURES

DISTRIBUTION—more common on the trunk in men and extremities in women. Typically occur in relatively non-pigmented areas in non-whites. Unusual primary sites for melanoma include CNS, eyes, mucosa (respiratory, GI, GU), palate, gingival, vulva and anus

SYMPTOMS

- **LOCOREGIONAL**—skin lesion (see *JAMA* series below)
- **METASTATIC**—depending on location (lung, GI tract, liver, brain, subcutaneous, skin, bone, heart)
- **PARANEOPLASTIC**—vitiligo, melanosis syndrome (slate gray skin discoloration), dermatomyositis

CLINICAL FEATURES (CONT'D)

gynecomastia, Cushing's, hypercalcemia, neurological

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE A MOLE OR A MELANOMA?

CHECKLIST ★ABCDE★—Asymmetry, **B**order irregularity, **C**olor variegation, **D**iameter >6 mm, **E**volution/ **E**nlargement (change in lesion)

REVISED 7-POINT CHECKLIST—change in size, change in color/irregular color, change in shape/irregular shape, presence of inflammation, diameter ≥7 mm, crusting or bleeding, sensory change (sens 79–100%, spc 30–37%, depending on how many criteria used)

	LR+	LR–
ABCDE Criteria for Melanoma		
Asymmetry	2.1	0.59
Border irregularity	2.1	0.59
Color variegation	1.6	0.59
Dimension >6 mm	2.3	0.17
Enlargement	11	0.18
Combination of ABCDE Criteria		
5 positive findings	98	–
≥4 positive findings	8.3	–
≥3 positive findings	3.3	–
≥2 positive findings	2.6	–
≥1 positive finding	1.5	–
0 findings	0.07	–

APPROACH—"using either checklist, misdiagnosing a melanoma as a benign lesion appears to be unlikely. The revised 7-point checklist has higher chance of classifying benign lesions as malignant. Non-dermatologists' examinations are less sensitive than those performed by dermatologists"

UPDATE—combination of increasing ABCDE criteria increases the likelihood of melanoma; enlargement of a skin lesion is the single most powerful univariate predictor

JAMA 1998 279:9
The Rational Clinical Examination.
McGraw-Hill, 2009

INVESTIGATIONS

BASIC

- **EXCISIONAL BIOPSY**—all lesions suspicious for melanoma should be biopsied with caution to obtain the total depth of the melanoma. Breslow depth is the most important prognostic indicator for patients

SPECIAL

- **LABS**—CBC, lytes, urea, Cr, LDH, AST, ALT, ALP, bilirubin as part of staging workup after pathology confirmation
- **IMAGING**—CXR as part of staging workup after pathology confirmation

DIAGNOSTIC AND PROGNOSTIC ISSUES

CLARK'S LEVELS (LIMITED UTILITY FOR SMALL LESIONS)

Level	TNM	5-year survival (%)
I	Intraepidermal (in situ)	100
II	Invasion into papillary dermis	85
III	Extensive invasion of papillary dermis	65
IV	Invasion into reticular dermis	50
V	Invasion into subcutaneous tissue	15

TNM STAGING 2009

T STAGE (Breslow depth/thickness)

- **T1** ≤ 1 mm
  - **T1a** = without ulceration and mitosis <1/mm^2
  - **T1b** = with ulceration or mitosis ≥1/mm^2
- **T2** = 1.01–2 mm
  - **T2a** = without ulceration
  - **T2b** = with ulceration
- **T3** = 2.01–4 mm
  - **T3a** = without ulceration
  - **T3b** = with ulceration
- **T4** > 4 mm
  - **T4a** = without ulceration
  - **T4b** = with ulceration

N STAGE

- **N1** = 1 LN
  - **N1a** = micronodal
  - **N1b** = macronodal

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

- **N2** = 2–3 LN
  - **N2a** = micronodal
  - **N2b** = macronodal
  - **N2c** = in-transit metastasis/satellite without metastatic nodes
- **N3** ≥ 4 nodes, or matted nodes, or in transit metastasis/satellites with metastatic nodes

M STAGE (lungs, bone, liver, skin, and essentially any organ. Biologically heterogeneous with variable course)

- **M1a** = distant skin, subcutaneous, or nodal metastasis with normal LDH
- **M1b** = lung with normal LDH
- **M1c** = visceral organs or elevated LDH

STAGE GROUPINGS

Stage	TNM @ = any	10-year survival
IA	T1aN0M0	95%
IB	T1b–T2aN0M0	85%
IIA	T2b–3aN0M0	70%
IIB	T3b–4aN0M0	60%
IIC	T4bN0M0	40%
III	T@N1–3 M0	
IIIA	T1a–4aN1aM0, T1a–4aN2aM0	70%
IIIB	T1b–4bN1aM0, T1b–4bN2aM0, T1a–4aN1bM0, T1a–4aN2bM0, T1–4aN2cM0	45%
IIIC	T1b–4bN1bM0, T1b–4bN2bM0, T1–4bN2cM0, T@N3M0	25%
IV	T@N@M1	10%

SENTINEL LYMPH NODE BIOPSY—usually done if primary melanoma is 1–4 mm thick or ulcerated

PROGNOSIS BY SITE OF METASTASIS—**M1a** = 62% 1-year survival, **M1b** = 53% 1-year survival, **M1c** = 33% 1-year survival

MANAGEMENT

PREVENTION—**sun avoidance** (sun-protective clothing, wide-brimmed hat, sunscreens)

SURVEILLANCE—particularly for high-risk individuals

STAGE I–III—standard of care is **wide local excision**. Mohs micrographic surgery may be used. Excision margin 1 cm for lesions ≤1 mm thick, 1–2 cm for lesions 1.01–2 mm, and 2 cm for lesions >2 mm thick). **Sentinel lymph node biopsy** for lesions >1 mm thick. If palpable node or sentinel LN positive, consider **lymph node dissection** and **adjuvant high-dose interferon α2b** (5 days/week IV × 4 weeks, then 3 days/week SC × 48 weeks). If extranodal extension, LN >3 cm, desmoplsatic lesions or extensive neurotrophism, consider **adjuvant radiation**. For locoregional recurrence, consider re-excision. **Follow-up** of these patients should include a complete review of systems including headache, visual changes, cough, lymph node examination, and an LDH and imaging to rule out metastasis for patients with deep melanomas. Patients should continue skin examinations at least semi-annually for new lesions as patients have a 3–5% chance of developing another melanoma

STAGE IV—**palliative systemic therapy** (for first line, consider ipilimumab or if BRAF 600 mutant, dabrafenib plus trametinib, dabrafenib alone, trametinib alone, or vemurafenib alone. Second line agents include pembrolizumab, dacarbazine, temozolomide, pacliataxel or carboplatin plus paclitaxel). **Palliative radiation** (if localized pain). **Excision** of solitary brain or lung metastasis is occasionally done

SPECIFIC ENTITIES

DYSPLASTIC NEVI—acquired moles characterized by cytologic atypia and architectural disorder. They remain dynamic throughout life, constantly appearing, changing, or disappearing

DYSPLASTIC NEVUS SYNDROME—melanoma in ≥2 blood relatives and dysplastic nevi in other family members

BASAL CELL CARCINOMA

- **PATHOPHYSIOLOGY**—the most common form of skin cancer. Although they rarely metastasize, basal cell carcinomas are locally destructive and must be removed
- **CLINICAL FEATURES**
  - **NODULAR SUBTYPE** (50–80%)—pearly semi-translucent papules with telangiectasias and central depression; may ulcerate crust or bleed
  - **SUPERFICIAL SUBTYPE** (>15%)—psoriasiform scaly plaque; most common on trunk and extremities
  - **PIGMENTED SUBTYPE** (6%)—more common in Latin Americans and Asians
  - **MORPHEAFORM SUBTYPE** (2–6%)—white sclerotic plaque, can mimic a scar; predilection to recur
- **RISK FACTORS**—history of prior sunburns (especially in childhood), radiation therapy, family history, immunosuppression, fair complexion, and red hair
- **TREATMENTS**—usually treated by either excision or electrodessication and curettage. However, if superficial they may be treated with topical imiquimod or photodynamic therapy

ACTINIC KERATOSIS

- **PATHOPHYSIOLOGY**—form after chronic sun exposure in susceptible individuals usually on the face, scalp, forearms, and dorsal hands. Actinic keratoses are foci of superficial keratinocyte dysplasia capable of evolving into squamous cell skin cancer
- **CLINICAL FEATURES**—thin pink to red papules and plaques with overlying scale, may sometimes contain focal pigment. They are most common on people with fair skin (type I or II) and occur with increased frequency in patients who are immunosuppressed or have received phototherapy
- **TREATMENTS**—cryotherapy for focal lesions. If diffuse damage is present, one may use topical imiquimod, 5-fluorouracil, diclofenac, trichloroacetic acid peels, and photodynamic therapy. If there is a thick component below the skin surface, one should consider a skin biopsy to rule out underlying squamous cell carcinoma

SQUAMOUS CELL CARCINOMA

- **PATHOPHYSIOLOGY**—second most common form of skin cancer. On average 0.5–5.2% of squamous cell carcinomas metastasize, but they are much more aggressive on mucosal surfaces such as the lip and in areas of previous irradiation and scarring
- **RISK FACTORS**—same as risk factors for actinic keratoses, plus HPV infection for genital lesions
- **CLINICAL FEATURES**—typically firm red scaly plaques that frequently become ulcerated and occur in areas of heavy sun exposure in fair-skinned individuals. Subtypes include
  - **BOWEN'S DISEASE**—squamous cell carcinoma in situ

SPECIFIC ENTITIES (CONT'D)

- **ERYTHROPLASIA OF QUEYRAT**—squamous cell carcinoma in situ of the penis
- **KERATOACANTHOMA**—rapidly developing volcano-like nodule that may spontaneously involute
- **VERRUCOUS CARCINOMA**—clinically and histologically resembles a wart

- **TREATMENTS**—surgical excision is the treatment of choice

SEBORRHEIC KERATOSIS

- **PATHOPHYSIOLOGY**—benign tumor of keratinocytes. Generally familial in nature
- **CLINICAL FEATURES**—benign skin colored to black papules and plaques with well-defined borders. They often have a warty surface and a stuck-on appearance. Seborrheic keratoses are most commonly located on the back but can occur on the head, neck, and extremities. It is important to try to differentiate seborrheic keratoses clinically from melanoma. The Leser–Trelat sign denotes the sudden onset of numerous pruritic seborrheic keratosis along with skin tags and acanthosis nigricans and may indicate underlying malignancy (adenocarcinoma of the stomach and lung, leukemia, lymphoma, Sezary syndrome)
- **TREATMENTS**—liquid nitrogen cryotherapy, curettage, or shave removal

SPECIFIC ENTITIES (CONT'D)

VERRUCA VULGARIS (COMMON WARTS)

- **PATHOPHYSIOLOGY**—a human papillomavirus (HPV) infection of keratinocytes. Lesions are benign but may cause cosmetic concern and are increased in immunocompromised individuals
- **CLINICAL FEATURES**—lesions are well-defined, firm papules or plaques with a hyperkeratotic cauliflower-like or flat surface. Lesions may have brown/black dots which represent thrombosed capillaries. Typically occur over extremities and genital area. Spontaneous resolution within 6 months for 30% of patients and 2 years for 65% of patients
- **TREATMENTS**—manual paring of the lesions, cryotherapy, topical salicylic acid (e.g. salicylate cream 40% daily with glutaraldehyde 10–25% daily), imiquimod, 5-fluorouracil, cantharidin, podophylin, laser therapy, and intralesional bleomycin

VITILIGO

- **PATHOPHYSIOLOGY**—autoimmune process against melanocytes. Differential diagnoses include tinea, leprosy, morphea, lichen sclerosus, post-inflammatory hypopigmentation, and chemicals
- **CLINICAL FEATURES**—hypopigmented patch(es)
- **TREATMENTS**—topical steroids, UV light

Cutaneous Lupus Erythematosus

DIFFERENTIAL DIAGNOSIS OF PHOTOSENSITIVITY

IATROGENIC (DRUGS)

- **AMIODARONE**
- **DIURETICS**—hydrochlorothiazide, loop diuretics
- **ANTIBIOTICS**—tetracycline
- **NSAIDs**
- **ANTINEOPLASTIC**—methotrexate, vincristine, 5-fluorouracil

INFLAMMATORY—SLE, dermatomyositis, rosacea

IDIOPATHIC—polymorphic light eruption, prurigo, actinic dermatitis, solar urticaria, chronic photosensitivity dermatitis

OTHERS—photocontact dermatitis, phytocontact dermatitis (celery, parsley, lime, lemon, yarrow), porphyria, xeroderma pigmentosum

CLINICAL FEATURES

CUTANEOUS MANIFESTATION OF SLE

- **MALAR RASH**— "butterfly rash" in up to 50% of lupus patients. Erythema in a malar distribution over the cheeks and bridge of the nose that spares nasolabial folds, especially after UV exposure
- **DISCORD LUPUS**—up to 50% of lupus patients. Discrete, erythematous, scaly plaques with follicular plugging over face, neck, and scalp, especially after UV exposure. May lead to central scars, atrophy, telangiectasias, and hyper-/hypopigmentation
- **SUBACUTE CUTANEOUS LUPUS**—up to 10% of lupus patients. Erythematous, slightly scaly papules that evolve into a papulosquamous or annular lesion over shoulders, forearms, neck, and upper torso. Usually no follicular plugging,

CLINICAL FEATURES (CONT'D)

hyperkeratosis, atrophy, pigment changes, and scarring

- **LUPUS PROFUNDUS**—firm, painful nodules over scalp, face, arms, chest, back, thighs, and buttocks
- **LUPUS TUMIDUS**—chronic violaceous papules and plaques or nodule lesions over areas exposed to the sun
- **BULLOUS LESIONS**—photosensitivity
- **LIVEDO RETICULARIS**—see SPECIFIC DISORDERS
- **NAIL LESIONS**—up to 25% of lupus patients. Changes include pitting, ridging, onycholysis and lunula (redness of half moon), periungual erythema
- **MUCOUS MEMBRANE ULCERS**
- **LUPUS ALOPECIA**

INVESTIGATIONS

BASIC

- **BLOOD TESTS**—CBCD, ANA, ENA, dsDNA

SPECIAL

- **SKIN BIOPSY**
- **PORPHYRIA WORKUP**—porphyrin, urine porphyrin

MANAGEMENT

TREATMENT UNDERLYING CAUSE—sun protection. Topical steroid ointments. Topical immunosuppressants (tacrolimus). Antimalarial (hydroxychloroquine). Systemic immunosuppressants

Related Topics
Systemic Lupus Erythematosus (p. 316)
Porphyria (p. 483)

SPECIFIC ENTITIES

CENTRAL FACIAL TELANGIECTASIA OR ERYTHEMA—common causes include rosacea, dermatomyositis, SLE, dermatitis (seborrheic, atopic, contact), glucocorticoid-induced dermal atrophy, flushing

TELANGIECTASIA—common causes include sun damage, aging, hypertension, alcoholism, diabetes, rosacea, amyloidosis, lupus, other rheumatic diseases, and ataxia telangiectasia

LIVEDO RETICULARIS

- **CAUSES**—**vascular** (polyarteritis, SLE, livedo vasculitis, cryoglobulinemia, antiphospholipid antibody syndrome, atherosclerosis, syphilis, TB), **hyperviscosity** (polycythemia, thrombocytosis, macroglobulinemia), **congenital**, **cerebrovascular disease** (Sneddon's syndrome), **idiopathic**
- **CLINICAL FEATURES**—reddish-cyanotic, reticular patches over the arms, legs, and torso, particularly in cold environments. May progress to vascular occlusion with ischemia and tissue infarction (livedo vasculitis with triad of purpuric macules, cutaneous nodules, and painful ulcerations)

PORPHYRIA CUTANEA TARDA

- **PATHOPHYSIOLOGY**—heterozygous deficiency of uroporphyrinogen decarboxylase, important for heme synthesis
- **ASSOCIATIONS**—hemochromatosis, alcohol, HCV, HIV, estrogens, smoking, hemodialysis
- **CLINICAL FEATURES**—photodistributed blistering or superficial skin erosion (commonly on back of hands)
- **TREATMENTS**—avoid exacerbating factors (alcohol, estrogens, iron supplements, drugs). Phlebotomy to reduce ferritin <20 ng/mL is first line. Chloroquine, hydroxychloroquine

Drug Eruptions

DIFFERENTIAL DIAGNOSIS

EXANTHEMS

- **ANTIBIOTICS**—penicillins, sulfonamides, erythromycin, gentamicin
- **ANTICONVULSANTS**
- **ALLOPURINOL**
- **GOLD**

URTICARIA, ANGIOEDEMA

- **IMMUNE IgE-MEDIATED**—penicillins, cephalosporins, sulfonamides, local anesthetic agents, radiocontrast, transfusion, latex

SPECIFIC ENTITIES (CONT'D)

- **NON-IMMUNE BRADYKININ-MEDIATED**—radiocontrast, ACE inhibitors
- **MAST CELL DEGRANULATION**—narcotics, muscle relaxants (atracurium, vecuronium, succinylcholine, curare), vancomycin

FIXED DRUG ERUPTION

- **LAXATIVES**—phenolphthalein
- **ANTIBIOTICS**—tetracyclines, sulfonamides, barbiturates
- **ANTI-INFLAMMATORIES**—NSAIDs, ASA photosensitivity

SPECIFIC ENTITIES (CONT'D)

- **DIURETICS**—hydrochlorothiazide, loop diuretics
- **ANTIBIOTICS**—tetracycline
- **ANTI-NEOPLASTICS**—methotrexate, vincristine, 5-fluorouracil

ERYTHEMA MULTIFORME, STEVENS–JOHNSON SYNDROME ★4A'S★

- **ALLOPURINOL**
- **ANTIBIOTICS**—sulfonamides, penicillins, cephalosporins
- **ANTICONVULSANTS**—phenytoin, carbamazepine, phenobarbital
- **ANTI-INFLAMMATORIES**—NSAIDs

CONTACT DERMATITIS—neomycin, benzocaine, paraben, ethylenediamine, formaldehyde, paraaminobenzoic acid

HYPERSENSITIVITY VASCULITIS

- **ALLOPURINOL**
- **DIURETICS**—furosemide, thiazide
- **ANTIBIOTICS**—penicillins, sulfonamides
- **OTHERS**—cimetidine, hydantoin

PIGMENTARY CHANGES

- **AMIODARONE**
- **ANTIBIOTICS**—tetracycline, minocycline, antimalarials
- **METALS**—silver, mercury, gold
- **OTHERS**—TCA, quinine, oral contraceptives

INVESTIGATIONS

SPECIAL

- **BLOOD TESTS**—CBCD (eosinophils), quantitative Ig (IgE increased), tryptase (marker of mast cell degranulation)
- **ALLERGY TESTING**—radioallergosorbent test, patch testing
- **SKIN BIOPSY**

MANAGEMENT

DISCONTINUE OFFENDING DRUG—see SPECIFIC ENTITIES for further details

SPECIFIC ENTITIES

EXANTHEMATOUS DRUG REACTION

- **PATHOPHYSIOLOGY**—the most common type of cutaneous drug reaction. Common offenders include penicillins, sulfonamides, carbamazepine, allopurinol and gold
- **CLINICAL FEATURES**—exanthematous rash usually appears within 14 days of drug initiation or 3 days of re-offending drug. The reaction is characterized by the development of symmetric, red, morbilliform rash almost always found on the trunk and extremities, which may be very pruritic. Usually lasts 1–2 weeks

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—identification and cessation of the offending drug. Oral antihistamines for relief of itching. Topical glucocorticoids may speed up recovery. Oral and IV steroids may be used for severe symptoms

URTICARIA AND ANGIOEDEMA

- **PATHOPHYSIOLOGY**—urticaria involves the development of highly pruritic pink wheals. Angioedema is subcutaneous tissue swelling, most prominent on the face (lips, eyelids) and tongue
- **TYPES**—**IgE-mediated type I hypersensitivity reactions** occur within minutes to hours in sensitized patients and are classically associated with penicillin as well as cephalosporins and sulfonamides. Hypotension, bronchospasm, and laryngeal edema may accompany the rash. **Immune-complex mediated reactions** usually occur within 12–36 h of drug exposure in a sensitized individual. Common offenders are penicillins and immunoglobulins. **Non-allergic forms** of urticaria and angioedema occur from drug-induced bradykinin release and/or mast cell degranulation. The reaction typically occurs within 20–30 min of drug administration. Common drugs include NSAIDs, opiates, ACE inhibitors, calcium channel blockers, and radiocontrast
- **TREATMENTS**—cessation of the offending drug. Antihistamines and oral steroids may be used. For acute, life-threatening reactions, ABCs, O_2, ***epinephrine*** 0.5 mL of 1:1,000 (1 mg/mL) IM, repeat q5min as needed (consider epinephrine 0.01–0.02 mg/h IV for severe/refractory anaphylaxis), NS 1–2 L IV bolus, ***salbutamol*** 2.5 mg NEB q5min PRN, ***dimenhydrinate*** 25–50 mg IV, **steroids** (*methylprednisolone* 125 mg IV or *dexamethasone* 20 mg IV). Consider vasopressors if severe shock. **Consult** anesthesia if anticipate difficult intubation or ENT if urgent tracheostomy required

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

- **PATHOPHYSIOLOGY**—an acute, pustular eruption that typically begins in the body folds and/or face and spreads over the trunk and extremities
- **CLINICAL FEATURES**—diffuse, sterile pustules with an edematous, erythematous background. Patients may appear ill with fever and leukocytosis. Most cases begin within 2–3 days of drug administration
- **TREATMENTS**—typically resolve within 2 weeks after the drug is stopped

SPECIFIC ENTITIES (CONT'D)

FIXED DRUG ERUPTION

- **PATHOPHYSIOLOGY**—the appearance of a solitary erythematous patch or plaque within 30 min to 8 h after ingestion of a drug. Offending agents include antibiotics (tetracyclines, sulfonamides), analgesics (NSAIDs, salicylates), and yellow dyes
- **CLINICAL FEATURES**—erythematous, edematous plaques with a grayish center or bullae over genitalia (most common), lips, tongue, face, and acral areas. Characterized by presence of post-inflammatory hyperpigmentation and the recurrence at exactly the same site with reexposure. Lesions may be accompanied by itching or burning
- **TREATMENTS**—cessation of the offending drug and application of topical steroid ointment

CONTACT DERMATITIS

- **PATHOPHYSIOLOGY**—due to topical agents or contact. Type IV hypersensitivity reaction (delayed cell mediated, T-cell activated)

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—erythematous, papular, urticarial, or vesicular pruritic plaques over area of exposure. Well-defined shape correlates with the offending contactant (e.g. nickel, tape, antibiotic ointment)
- **TREATMENTS**—identify and avoid causative agent(s)

HYPERSENSITIVITY VASCULITIS

- **CLINICAL FEATURES**—macules/papules on lower extremities or back evolving into palpable purpura, bullae, and/or necrosis. May also have fever, myalgia, and arthralgia
- **ACR CRITERIA**—age at disease onset >16 years, medication at disease onset, palpable purpura, morbilliform rash, biopsy including arteriole and venule. Need three of five criteria (sens 71%, spc 84%)
- **TREATMENTS**—discontinue offending drug

Related Topics
Antibiotics (p. 282)
Penicillin Allergy (p. 288)

Erythema Nodosum

DIFFERENTIAL DIAGNOSIS OF PAINFUL NODULES

PANNICULITIS—erythema nodosum, erythema induratum, Weber–Christian disease (relapsing febrile nodular panniculitis)
INFECTIONS—bacteria, fungi
CUTANEOUS VASCULITIS
SUPERFICIAL THROMBOPHLEBITIS

PATHOPHYSIOLOGY

CAUSES OF ERYTHEMA NODOSUM

INFECTIOUS—bacterial (Streptococcal, Yersiniosis), atypical (*Chlamydia pneumoniae*), TB, fungal (Coccidioidomycosis, Histoplasmosis, Blastomycosis), leprosy
INFLAMMATORY—IBD, SLE, Behcet's
INFILTRATIVE—sarcoidosis, Hodgkin's
IATROGENIC—oral contraceptive pills, omeprazole, montelukast
IDIOPATHIC

CLINICAL FEATURES

TYPICAL PRESENTATION—painful, erythematous nodules on the anterior surfaces of bilateral shins and sometimes thighs, trunk, and upper

CLINICAL FEATURES (CONT'D)

bruise-like lesions that resolve without scarring over a 2–8-week period. Other symptoms include polyarthralgias, fever, and malaise. Presence of GI symptoms and/or hilar adenopathy may help in narrowing differential

INVESTIGATIONS

BASIC

- **LABS**—CBCD, antistreptolysin-O titer, ANA
- **MICROBIOLOGY**—wound C&S, throat C&S (for *Streptococcus*), TB skin test
- **IMAGING**—CXR

SPECIAL

- **DEEP INCISIONAL BIOPSY**

MANAGEMENT

SYMPTOM CONTROL—**NSAIDs**, **potassium iodide**, **glucocorticoids** (beware of TB)
TREAT UNDERLYING CAUSE

Related Topics
Tuberculosis (p. 279)
Fungal Infections (p. 298)
Sarcoidosis (p. 482)

Clubbing

DIFFERENTIAL DIAGNOSIS

RESPIRATORY—lung cancer, lung abscess, bronchiectasis, cystic fibrosis, empyema, mesothelioma, idiopathic pulmonary fibrosis, asbestosis
CARDIAC—cyanotic heart disease, subacute endocarditis
GI—colon cancer, esophageal cancer, inflammatory bowel disease, Celiac disease, cirrhosis
OTHERS—hyperthyroidism (thyroid acropachy), hemoglobinopathies, local vascular disease, familial

PATHOPHYSIOLOGY

MECHANISM—proliferation of the connective tissue between the nail matrix and the distal phalanx
STAGES—periungual erythema → spongy nail bed → loss of Lovibond's angle → increased phalangeal depth ratio → hypertrophic osteoarthropathy

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE CLUBBING?
INSPECTION—**nail fold profile angle** (angle that nail projects from nail fold, normal ≤176°, simplified to straight line of <180° for clinical use), **hyponychial nail-fold angle** (angle that nail directs toward the nail tip, normal ≤192°, simplified to <190° for clinical use), **phalangeal depth ratio** (distal phalangeal finger depth/interphalangeal finger depth ratio normal ≤1), **Schamroth sign** (normal = diamond)
PALPATION—floating nail bed elicited by rocking the distal and proximal nail back and forth
APPROACH—"the profile angle and phalangeal depth ratio can be used as quantitative indices to assist in identifying clubbing. In individuals without clubbing, values for these indices do not exceed 192°, and 1.0, respectively. Inter-observer

CLINICAL FEATURES (CONT'D)

agreement by clinicians is highly variable (κ values 0.39–0.90). Because of the lack of an objective diagnostic standard, accuracy of physical examination for clubbing cannot be determined. The accuracy of clubbing as a marker of specific underlying disease has been determined for lung cancer (LR+ 3.9 with phalangeal depth ratio >1.0) and for inflammatory bowel disease (LR+ 2.8 and 3.7 for active Crohn's disease and ulcerative colitis, respectively)"
UPDATE—clubbing in cystic fibrosis predictive of hypoxemia (LR+ 3.2)

JAMA 2001 286:3
The Rational Clinical Examination. McGraw-Hill, 2009

INVESTIGATIONS

BASIC
- **IMAGING**—CXR

SPECIAL
- **CARDIAC WORKUP**—ECG, echocardiogram
- **OTHER ETIOLOGY WORKUP**—CBCD, TSH, AST, ALT, ALP, bili

MANAGEMENT

TREAT UNDERLYING CAUSE

SPECIFIC ENTITIES

HYPERTROPHIC OSTEOARTHROPATHY—clubbing and periarticular pain and swelling, most often affecting the wrists, ankles, and knees. Associated with bronchogenic cancer, chronic pulmonary infections, cystic fibrosis, and cyanotic congenital heart disease

Related Topics
Celiac Disease (p. 139)
Inflammatory Bowel Disease (p. 135)
Lung Cancer (p. 203)

Dupuytren's Contracture

DIFFERENTIAL DIAGNOSIS

DIABETIC CHEIROARTHROPATHY (usually all four fingers)
INTRINSIC JOINT DISEASE
DUPUYTREN'S CONTRACTURE
VOLKMANN'S ISCHEMIC CONTRACTURE
TRAUMATIC SCARS
PALMAR FASCIITIS—malignancy (usually bilateral)

PATHOPHYSIOLOGY

RISK FACTORS—alcoholism, smoking, diabetes, repetitive hand motions/vibrations, reflex sympathetic dystrophy, positive family history, Scandinavian/Northern European descent
4 STAGES—progressive fibrosis of the palmar fascia → nodules form on the palmar fascia → flexion deformity → fibrosis of dermis leads to skin thickening

CLINICAL FEATURES

HISTORY—finger stiffness (duration, pain, function), past medical history (alcohol, diabetes, smoking, HIV), occupational history
PHYSICAL—most commonly involves the fourth and fifth digits. Triangular puckering of the dermal tissue over the flexor tendon just proximal to the flexor crease of the finger (earliest sign), skin blanching on active finger extension, palpable and visible nodules along flexor tendons, mild tenderness over nodules, fixed flexion contractures, reduced range of motion, tender knuckle pads over the dorsal aspect of the PIP joints

MANAGEMENT

SYMPTOM CONTROL—padded gloves, stretching exercises for mild disease. Triamcinolone or lidocaine injection for moderate disease. Radiation, needle aponeurotomy, collagenase injection or surgery for severe disease

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GERIATRICS

Diana Rucker

Geriatric-Specific Issues

THE FRAIL ELDERLY

THE CONCEPT OF FRAILTY—refers to a state of functional decline in which loss of physiologic reserve makes an individual susceptible to disability from minor stresses. Several definitions of frailty have been proposed. The phenotypic definition validated in the Cardiovascular Health Study is widely accepted and is comprised of 5 clinical characteristics: (1) self reported exhaustion, (2) decline in activity level, (3) weight loss, (4) impaired strength and (5) slow gait. 0 points = "robust" and ≥3 suggests frail

POTENTIAL PRECIPITANTS—acute illness, infections, infarction, medications, social stress, environmental changes, and surgical intervention. Patients with frailty are at higher risk of complications, such as increased mortality, morbidity, and rates of institutionalization when faced with these precipitants

COMPREHENSIVE GERIATRICS ASSESSMENT

In addition to a focused history and physical, special attention should be paid to the following domains, which provide important information for the geriatric assessment:

FUNCTIONAL HISTORY—activities of daily living ADLs (mobility, bathing, dressing, toileting, transferring, maintaining continence, and feeding) and instrumental activities of daily living (IADLs, transportation, shopping, phoning, laundry, cooking, accounting, housekeeping, medications)

GERIATRIC SYNDROMES/GIANTS—falls (number and mechanism in last year) and mobility, presence of osteoporosis and previous fractures, chronic pain, pressure sores, sleep patterns, mood and behavioral problems, continence (urinary and fecal), nutrition (appetite and weight loss), hearing and visual impairment

COMPREHENSIVE GERIATRICS ASSESSMENT (CONT'D)

COGNITIVE HISTORY—memory, language, executive function, praxis and visuospatial domains. Inquire about behavioral problems (anger, withdrawn, hoarding sundowning) and safety concerns (driving, using appliances, potential of abuse)

COMORBID CONDITIONS—in addition to the geriatric syndromes, inquire about the number and severity of co-existing diseases that are either life threatening or function limiting

POLYPHARMACY—number of medications, potential medications that can cause delirium and other significant side effects, adherence, assistance with medications, drug interactions (p. 436)

SOCIAL HISTORY—living situation, education, work, family, caregivers at home (ask directly about caregiver stress or burn out), financial stability, access to transportation, personal directives

COGNITIVE EXAMINATION—screen for cognitive impairment with the mini-mental state (MMSE) exam or Montreal Cognitive Assessment (MoCA). MMSE is limited in assessing executive function which can further be evaluated with clock drawing, Frontal Assessment Battery (FAB) or and EXIT test. Delirium can be assessed with the CAM score (see DELIRIUM p. 432)

COMPREHENSIVE GERIATRIC MANAGEMENT

INTERPROFESSIONAL TEAMS—often require interdisciplinary teams consisting of geriatricians, nurses, social workers, physiotherapists, occupational therapists, pharmacists, registered dieticians, speech-language therapists, recreational therapists, psychologists, and family

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COMPREHENSIVE GERIATRIC MANAGEMENT (CONT'D)

Discipline	Task(s)
Dieticians	Nutrition and diet
Nurses	Education and assistance with ADLs, IADLs
Occupational therapists	Cognitive and functional assessments, ADL training
Pharmacists	Medication use
Physicians	Disease management, symptom management, communication and decision making, care planning
Physiotherapists	Training to increase range of motion, strength, endurance, coordination, mobility
Recreational therapists	Maintenance of social roles
Social workers	Counseling, evaluation, and disposition within community
Speech language therapists	Training in communication and therapy for swallowing disorders

HEALTH CARE AND FINANCIAL PROXY

ADVANCE DIRECTIVE (living will)—a document that is created when patient is competent. Allows direction of their care in future (e.g. regarding tube feeding, resuscitation status) if and when they are no longer capable of expressing their own wishes

PERSONAL DIRECTIVE—agent assigned when patient competent so that if they become incompetent, agent can act on patient's behalf regarding decisions for personal care and accommodation

POWER OF ATTORNEY—agent assigned when patient competent so that if they become incompetent, agent can act on patient's behalf regarding finances

GUARDIANSHIP—created when patient is incompetent and personal directive not available. Guardian assists with decisions regarding personal care and accommodation

TRUSTEESHIP—created when patient is incompetent and power of attorney not available. Trustee assists with finances

COMPETENCY ASSESSMENT

ENSURE IT IS NECESSARY—usually requires a trigger. E.g. patient is no longer managing money wisely, needs long term care placement but not willing to go

DIAGNOSED PHYSICAL/MENTAL ILLNESS—chronic vs. acute

OBTAIN RELEVANT COLLATERAL INFORMATION—reliable? Ask what concerns them (ADLs, financial)

COMPETENCY ASSESSMENT (CONT'D)

PERFORM FORMAL TESTING—ask patient details about comorbidities, ADLs, finances, medical condition, living will. Are their details consistent with reality?

The four elements required for capacity are

1. Understanding: the ability to comprehend, retain and recall information regarding nature of involvement, risks, benefits, and alternatives
2. Appreciation: the ability to relate the information above to the patient's own situation
3. Reasoning: the ability to weigh the risks and benefits, and consider alternatives
4. Expression: the ability to articulate a choice

INFORM AND ACT

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE MEDICAL DECISION MAKING CAPACITY?

	LR+	LR–
Physician Clinical Judgment	7.9	0.61
Measures of Cognitive Ability		
MMSE <16	12	–
MMSE <20	6.3	–
MMSE 20–24	0.87	–
MMSE >24	0.14	–
Capacity Assessment Instruments		
Aid to Capacity Evaluation (ACE)	8.5	0.21
Hopkins Competency Assessment Test (HCAT)	54	0
Understanding Treatment Disclosure (UTD)	6.0	0.16

COMPETENCY ASSESSMENT (CONT'D)

APPROACH—physicians frequently do not identify patients with incapacity, although capacity is necessary for informed consent. Capacity can be optimized by treating reversible disorders. Measures of cognition (e.g. MMSE) correlate with capacity but are not the only criterion. Multiple instruments are available for

COMPETENCY ASSESSMENT (CONT'D)

capacity assessment; the ACE instrument (understanding the problem, treatment proposed and alternatives, option to refuse treatment, possible consequences of accepting and not accepting treatment, presence of depression and psychosis) has been validated

JAMA 2011 306:4

Dementia and Cognitive Impairment

DIFFERENTIAL DIAGNOSIS

PRIMARY PROGRESSIVE DEMENTIA

- **ALZHEIMER'S**—general sequence of changes include mood alterations and slow progressive cognitive decline; primarily affecting memory, language and visuospatial domains early on; early motor symptoms rare but may have apraxia later; loss of functional autonomy, neuropsychiatric manifestations, and parkinsonism may be seen in more advanced disease. CT may show white matter change, mostly a diagnosis of exclusion, but accounting for 60% of dementias
- **VASCULAR**—acute stepwise or slow progressive decline; may have focal neurological deficits; mini-mental state examination patchy; CT may show white matter change; pure vascular dementia uncommon; more frequently occurs with Alzheimer's like dementia (mixed vascular)
- **PARKINSON'S**—Parkinson's disease diagnosed for more than one year prior to cognitive onset; slow decline; Parkinson's patients have 6× increased risk for dementia
- **LEWY BODY**—progressive memory decline, parkinsonism, visual hallucinations, fluctuating cognition (especially attention/alertness), visuospatial domain often markedly impaired, supportive features include

DIFFERENTIAL DIAGNOSIS (CONT'D)

adverse hypersensitivity to typical antipsychotic medications, syncope, falls, delusions, and sleep disturbance

- **FRONTOTEMPORAL**—age usually <60; behavioral symptoms noticeable before cognitive impairment disinhibited or passive presentation, impaired judgment, significant social indifference, declining hygiene, prominent language deficits but amnesia less noticeable early on; early primitive reflexes/incontinence, late akinesia/rigidity/tremor, impaired executive function, MMSE may be normal; CT shows frontal temporal atrophy
- **PRION DISEASE**—Creutzfeldt–Jakob disease

POTENTIALLY REVERSIBLE DEMENTIA (<1%)

- **METABOLIC**—alcoholism, vitamin B12, hypothyroidism
- **STRUCTURAL**—normal pressure hydrocephalus (NPH), subdural hemorrhage, neoplastic, vascular
- **INFECTIONS**—chronic meningitis, HIV, neurosyphilis, Whipple's
- **INFLAMMATORY**—vasculitis, Hashimoto encephalitis, multiple sclerosis

DEMENTIA MIMICS—depression, delirium, developmental disorder, age-associated memory impairment

CLINICAL FEATURES

DISTINGUISHING FEATURES BETWEEN VARIOUS TYPES OF DEMENTIA

	Alzheimer's	Vascular	Fronto-temporal
Physical findings	Relatively normal	Focal neurological deficits	Disinhibited or passive, primitive reflexes
MMSE	Memory recall affected early on, language and visuospatial deficits	Patchy changes	May be normal
MOCA, Clock drawing, FAB, Exit test		Early executive loss	Early executive loss
CT head	White matter changes	White matter changes	Frontal temporal atrophy

Abbreviations: FAB, Frontal Assessment Battery; MOCA, Montreal Cognitive Assessment

Related Topics
Delirium (p. 432)
Parkinson's disease (p. 362)
Stroke (p. 337)
Vitamin B12 deficiency (p. 459)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE DEMENTIA?

MINI-MENTAL STATE EXAMINATION (MMSE)—orientation to place (5), time (5), immediate and delayed recall (6), spell "WORLD" backward (5), 3 step command (3), name two objects (2), close your eyes (1), repeat sentence "No, if's, and's, or but's" (1), write a sentence (1), intersecting pentagons (1). Maximum score is 30, generally <24 is impaired but varies with education and age

MEMORY IMPAIRMENT SCREEN—recall four objects (an animal, a city, a vegetable, and a musical instrument). Two points for free recall of each object and one point if prompting needed ("Tell me the name of the city."). Maximum score is 8. Takes 4 min

SELECTED TOOLS

	LR+	LR–
MMSE	6.3	0.19
Reports from an informant that the patient has memory loss	6.5	
Memory impairment screen	33	0.08
Clock drawings	1.2–7.7	0.13–0.71

APPROACH—"to detect cognitive impairment of at least moderate severity, consider the mini-mental state examination. The Hopkins Verbal Learning Test or the Word List Acquisition Test may be used to screen for mild impairment in highly educated patient. If very little time is available, consider the Memory Impairment Screen or the Clock Drawing Test. If plenty of time is available, consider the Cambridge Cognitive Examination, Modified Mini-Mental State Examination, Community Screening Interview for Dementia, or the Montreal Cognitive Assessment"

JAMA 2007 297:21

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, creatinine, glucose, Ca, TSH, vitamin B12
- **IMAGING**—head CT

SPECIAL

- **FURTHER DEMENTIA WORKUP**—AST, ALT, ALP, bilirubin, RBC folate, VDRL, HIV serology, urine collection for heavy metals

DIAGNOSTIC ISSUES

DSM V CRITERIA FOR NEUROCOGNITIVE DISORDERS (preferred term over dementia)

MAJOR NEUROCOGNITIVE DISORDER

A. A decline in one or more cognitive domains: learning and memory, language, executive function, complex attention, perceptual-motor or social cognition
B. Cognitive deficits must impair at least one IADL
C. Cognitive deficits do not occur during delirium and are not better explained by another psychiatric disorder

MINOR NEUROCOGNITIVE DISORDER

A. A modest decline in one or more cognitive domains: learning and memory, language, executive function, complex attention, perceptual-motor or social cognition
B. Cognitive deficits do not interfere with IADLs, although greater effort may be required
C. Cognitive deficits do not occur during delirium and are not better explained by another psychiatric disorder

MINI-MENTAL STATE EXAMINATION (MMSE)—adjusted based on age and education. An abnormal test may indicate the presence of dementia, delirium, or depression. Traditional threshold for MMSE ≤23 suggests dementia (LR+ 6–8) in the absence of delirium. Newer thresholds: ≤20 rules in dementia (LR+ 14.5, sens 39–69%, spc 93–99%), ≥26 rules out dementia (LR+ 0.1), 21–25 inconclusive (LR+ 2.2)

HACHINSKI ISCHEMIC SCORE

- **SCORING**—abrupt onset (2), stepwise progression (1), fluctuating course (2), nocturnal confusion (1), relative preservation of personality (1), depression (1), somatic complaints (1), emotional incontinence (1), history of hypertension (1), history of strokes (2), evidence of associated atherosclerosis (1), focal neurological symptoms (2), focal neurological signs (2)
- **UTILITY**—if score <4, likely Alzheimer's disease; if >7, likely vascular dementia

DIAGNOSTIC ISSUES (CONT'D)

CLOCK DRAWING—a test of constructional apraxia with many technical variants. The Wolf–Klein method provides patient with paper and preprinted circle (4 in. in diameter) and instructions to "draw a clock." The time must always be stated as "10 after 11". "Normal" clock has numbers clockwise in correct order and near the rim, even without hands on clock. Abnormal clock drawing argues for dementia (LR+ 5.3). Normal clock drawing not useful (as half of demented patients can produce normal clock)

CRITERIA FOR PERFORMING CT HEAD—age <60, rapid (1–2 months) unexplained decline in cognition or function, dementia of short duration (<2 years), unexplained neurological symptoms (e.g. new onset headache or seizures), early incontinence/gait disorder (NPH), recent head trauma, history of cancer, use of anticoagulants or history of bleeding disorder, new localizing signs, unusual or atypical cognitive symptoms or presentation (e.g. progressive aphasia)

CMAJ 1999 160:12; Canadian Consensus Conference on Dementia

MANAGEMENT

RISK REDUCTION—**anti-hypertensive** (see HYPERTENSION p. 65), **dyslipidemia treatment** (see DYSLIPIDEMIA p. 73)

DISEASE MANAGEMENT—**anticholinesterase** may be considered for Alzheimer's disease and include *donepezil* 5–10 mg PO qhs, *rivastigmine* 1.5–6 mg PO BID, and *galantamine ER* 8–24 mg daily. Avoid if seizures, cardiac conduction problems, significant asthma, COPD, or recent GI bleed. *Memantine* 5–10 mg PO BID may be used as a single agent or as add-on therapy to cholinesterase inhibitor

SYMPTOM MANAGEMENT—treat problem behaviors with non-pharmacological and pharmacological approaches (trazodone, atypical antipsychotics). Treat co-existing depression

TUBE FEEDING—generally not recommended for advanced dementia because of increased complications without evidence of clinical benefit (e.g. survival, quality of life, prevention of aspiration pneumonia, reduction of pressure sores or infections, functional improvement)

MANAGEMENT (CONT'D)

SPECIFIC ENTITIES

LESS COMMON CAUSES OF DEMENTIA

- **NORMAL PRESSURE HYDROCEPHALUS (NPH)**
  - **PATHOPHYSIOLOGY**—inflammation and fibrosis of the arachnoid granulations → decreased absorption of CSF → hydrocephalus → normal opening pressure but elevated pressure over periventricular white matter tracts
  - **CAUSES**—idiopathic or secondary, e.g. subarachnoid hemorrhage, chronic meningitis
  - **CLINICAL FEATURES**—classic triad of gait apraxia (magnetic gait as feet are stuck to floor), urge incontinence, and cognitive decline. Also may have postural instability, lower extremity spasticity, hyperreflexia, and extensor plantar responses
  - **DIAGNOSIS**—clinical diagnosis and MRI. Improvement of gait or cognition 1 h after removal of 30–50 mL of CSF can be helpful for diagnosis (Fisher test, PPV 90–100%, NPV 30–50%). An improvement also predicts responsiveness to shunting
  - **TREATMENTS**—lumbar puncture, shunts (ventriculoperitoneal, ventriculoatrial, lumboperitoneal)
- **PARKINSON'S-PLUS SYNDROMES**—includes progressive supranuclear palsy, multiple system atrophy and corticobasal ganglionic degeneration
- **CREUTZFELDT–JAKOB DISEASE**—rapid progression, characteristic EEG, myoclonic jerks, and expected death in 6–12 months
- **HUNTINGTON'S DEMENTIA**—autosomal dominant with incomplete penetrance; premorbid DNA testing quantifies risk, severity, and age of onset
- **CORTICONUCLEAR DEGENERATION**—marked visual–spatial impairment, substantial apraxia, but memory impairment less noticeable

Delirium

NEJM 2006 354:11

DIFFERENTIAL DIAGNOSIS

★DIMS★

DRUGS ★ABCD★

- **ALCOHOL**—intoxication, withdrawal, Wernicke–Korsakoff syndrome
- **ANTICHOLINERGICS**—atropine, benztropine, scopolamine
- **ANTIDEPRESSANTS**—SSRIs, TCAs
- **ANTICONVULSANTS**—carbamazepine, phenytoin, valproate, phenobarbital
- **ANALGESICS**—opioids, NSAIDs, steroids
- **ANTIBIOTICS**—penicillins, quinolones, sulfonamides, isoniazid, rifampin, streptomycin, chloroquine, acyclovir
- **ANTI-HISTAMINES**—cimetidine, famotidine, ranitidine
- **BENZODIAZEPINES AND BARBITURATES**—intoxication, withdrawal
- **CARDIAC**—amiodarone, β-blockers, digoxin, diuretics
- **DOPAMINE AGENTS**—amantadine, bromocriptine, levodopa

INFECTIOUS—pneumonia, UTI, meningitis, encephalitis, abscess, sepsis

METABOLIC

- **ORGAN FAILURE**—hepatic, azotemia, hypothyroidism or thyrotoxicosis, hypoxia, hypercapnia, hypothermia, hypertensive
- **ELECTROLYTE IMBALANCE**—ketoacidosis, glucose (hypo, hyper), hyponatremia, hypernatremia, hypomagnesemia, hypercalcemia

STRUCTURAL

- **HEMORRHAGE**—subarachnoid, epidural, subdural, intracerebral
- **STROKE**—basilar
- **TUMOR**
- **ABSCESS**

SEIZURES—non-convulsive status epilepticus (NCSE), post-ictal

PATHOPHYSIOLOGY

HOSPITALIZATION—hospitalized patients, particularly the elderly, are at high risk of developing delirium. The prevalence of delirium in geriatric patients on admission to hospital is 14–24%. The estimated incidence is up to 40% on the medical ward, 7–26% for general surgery, 29–42% for vascular surgery, 8–42% for cardiac surgery, and 16–62% for orthopedic surgery

FRAILTY IN ELDERLY—limited reserve so easily tipped over by any event, leading to delirium

DELIRIUM SUBTYPES

- **HYPERACTIVE DELIRIUM**—characterized by agitation and/or hallucinatory symptoms
- **MIXED DELIRIUM**—variable course with alternating hyperactive and hypoactive features. A majority of patients with delirium fall under this category
- **HYPOACTIVE DELIRIUM**—characterized by excessive drowsiness and decreased level of consciousness. May mimic depression

COMPLICATIONS—delirium can have a negative impact on patients' quality of life, symptom expression, emotions, and decision-making ability. Delirium also prolongs hospitalization and is associated with a poor prognosis and caregiver distress

DISTINGUISHING FEATURES BETWEEN DELIRIUM AND DEMENTIA

	Delirium	Dementia
Onset	Abrupt	Insidious
Course	Fluctuating, usually reversible	Slowly progressive and usually irreversible
Duration	Days to weeks	Years
Level of consciousness	Hyperactive or hypoactive	Affected in late stages
Attention span	Often affected	Affected in late stages
Orientation	Usually affected	Usually affected
Memory	May be affected	Usually affected
CT head	May be normal; structural changes	White matter changes, atrophy

CLINICAL FEATURES

CONFUSION ASSESSMENT METHOD (CAM)—positive test argues strongly for delirium (LR + 10.3) and negative test argues against delirium (LR – 0.2). Positive test requires both major criteria 1+2 *and* either of the minor criteria 3 or 4 ★**AIDS**★

1. **ACUTE ONSET AND FLUCTUATING CONFUSION**—abnormal behaviors come and go, ↑/↓ severity
2. **INATTENTION**—difficulty focusing/difficulty following conversation (serial subtraction with distraction)
3. **DISORGANIZED THINKING**—rambling, irrelevant, illogical conversation
4. **SENSORIUM CHANGE (ALTERED LOC)**—agitated, hyperalert, lethargic, stuporous, or comatose

EXAMINATION OF THE DELIRIOUS PATIENT—in addition to general physical and neurological examinations, obtain a baseline mini-mental state examination (useful for monitoring)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, Ca, urinalysis
- **IMAGING**—CXR, head CT
- **MICROBIOLOGY**—urine C&S, blood C&S (if any fever)

SPECIAL

- **METABOLIC WORKUP**—TSH if suspect thyroid disease, AST, ALT, ALP, bilirubin, INR, PTT, NH_4 if suspect liver disease, Mg, PO_4
- **CARDIAC WORKUP**—ECG, CK, troponin if suspect ACS
- **SEIZURES WORKUP**—EEG
- **DRUG OVERDOSE WORKUP**—medication serum levels (e.g. digoxin, phenytoin salicylate, acetaminophen), alcohol level, serum osmolality (osmolar gap)
- **MENINGITIS WORKUP**—lumbar puncture

DIAGNOSTIC ISSUES

PERSISTENT DELIRIUM—if delirium persists despite basic workup, think through differential diagnosis again (VERY CAREFULLY). Ask caregivers/family about baseline cognitive changes or pre-existing sundowning. Also consider dehydration, depression, urinary/fecal retention, alcohol or benzodiazepine withdrawal, abscess, sleep deprivation, environmental factors (i.e. hospitalization) as potential contributors. Inadequate pain control has also been proposed as a precipitant of delirium

Related Topics
Alcohol Withdrawal (p. 117)
Hypercalcemia (p. 402)
Meningitis (p. 269)
Metabolic Acidosis (p. 87)
Overdose (p. 115)

MANAGEMENT

PREVENTION—ensure adequate O_2, fluid and electrolyte balance, pain management, reduction in use of psychoactive drugs, bowel and bladder function, nutrition, early mobilization, prevention of postop complications, appropriate environmental stimuli, and treatment of symptoms of delirium

TREAT UNDERLYING CAUSE—discontinue offending medications. Delirium may take days/weeks to resolve even after the precipitating cause is removed and treated

NON-PHARMACOLOGICAL MEASURES—reduce noise, orient patient frequently, early mobilization, provide proper hearing and visual aids, provide clock/calendar and familiar objects (personal photos) and people (family), supervision for meals, restoration of day–night cycle (optimal lighting during day, promote sleep hygiene at night), avoidance of unnecessary interventions (physical or chemical restraints, urinary catheters, central lines)

PHARMACOLOGICAL MEASURES—**neuroleptics** for agitated patient (*haloperidol* 0.5–4 mg PO/IV/SC q4–6 h and q1h PRN, *chlorpromazine* 12.5-100 mg IV q4h and q1h PRN, *loxapine* 2.5–5 mg PO/SC BID and q6h PRN, *risperidone* 0.25 mg PO BID PRN, *olanzapine* 2.5–10 mg PO daily PRN, *quetiapine* 25 mg PO BID PRN), **benzodiazepines** may precipitate or worsen delirium and should generally be avoided except for patients with alcohol or benzodiazepine withdrawal, or those with severe agitated delirium despite high doses of neuroleptics (*lorazepam* 0.5–2 mg PO/SL/IV daily-QID PRN)

TREATMENT ISSUES

CONSENT FOR TREATMENT—if patient delirious and need to clarify direction of care, try to find agent for personal directive and/or proxy. If not available, consider calling closest family to discuss treatment options

Falls

JAGS 2000 48:8; NEJM 2003 348:1

DIFFERENTIAL DIAGNOSIS

SYNCOPE—neurogenic, cardiogenic, neurocardiogenic
DROP ATTACKS—transient vertebrobasilar insufficiency
POSTURAL HYPOTENSION
CONFUSION—delirium
DIZZINESS—vertigo, dysequilibrium
FALLS—accidental, imbalance

PATHOPHYSIOLOGY

PREDISPOSITION TO FALLS IN ELDERLY—multi-factorial in nature; 50% of patients who fall do so repeatedly. Multiple falls are a marker for other underlying factors, including chronic diseases and functional disability

- **HIGHER CORTICAL/CNS**—decreased reaction time
- **VESTIBULAR SYSTEM**—decreased balance
- **VISUAL SYSTEM**—presbyopia, decreased peripheral vision, and accommodation
- **AUTONOMIC SYSTEM**—postural hypotension
- **SOMATOSENSORY SYSTEM**—decreased sensation, proprioception, vibration perception
- **MUSCULOSKELETAL SYSTEM**—weakness
- **GAIT INCOORDINATION**—Parkinson's, cerebellar ataxia, stroke, NPH
- **MEDICATIONS** (strongest risk factor for falls)—SSRIs, TCAs, neuroleptics, anticonvulsants, benzodiazepines, class IA antiarrhythmics, narcotics
- **ENVIRONMENT**
- **PRECIPITANTS**—infection, infarction, medications, social stress

COMMUNITY DWELLING—41% of falls secondary to environment (trips, slips), 13% weakness or gait/balance disorder

NURSING HOME DWELLING—26% of falls secondary to weakness, gait/balance disorder, 16% environment related

COMPLICATIONS—institutionalization, fear of recurrent falls, prolonged immobility (risk for dehydration, pressure sores, pneumonia, rhabdomyolysis), and death

CLINICAL FEATURES

HISTORY—★**SPLAT**★ **S**ymptoms associated with fall (circumstances, onset, frequency), **P**revious falls, **P**ast medical history, **L**ocation, **A**ctivity preceding fall, **T**oxins (meds), and **T**rauma
PHYSICAL—vitals (postural HR and BP, temperature), cardiovascular (murmurs, rhythm, volume status), respiratory (adventitious sounds), musculoskeletal (strength in knee/hip extensors, joint stability and range of motion, pain, feet, footwear, walking aids), neurologic (focal signs, vision/hearing, cerebellar, sensory), cognitive exam (MMSE, CAM)

PERFORMANCE-ORIENTED EVALUATION OF GAIT AND BALANCE

- **TIMED UP AND GO TEST**—rise from chair, walk 10 ft, turn, and return to chair. Should finish in less than 10 s. If takes >20 s, further evaluation required
- **TINETTI'S PERFORMANCE-ORIENTED ASSESSMENT (POMA)**—easy to administer, incorporates gait, and balance scales to identify high risk of falls, score ≤20/28 predictive of recurrent falls

RATIONAL CLINICAL EXAMINATION SERIES: WILL MY PATIENT FALL?

	LR+
Fallen in the past year	2.3–2.8
Clinically detected abnormalities of gait or balance	1.7–2.4
Age, visual impairment, medication variables, decreased activities of daily living, and impaired cognition did not consistently predict falls across studies. Orthostatic hypotension did not predict falls after controlling for other factors	

APPROACH—"screening for risk of falling during the clinical examination begins with determining if the patient has fallen in the past year. For patients who have not previously fallen, screening consists of an assessment of gait and balance. Patients who have fallen or who have a gait or balance problems are at higher risk of future falls"
JAMA 2007 297:1

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, TSH, CK, ESR, urinalysis
- **IMAGING**—head CT

SPECIAL

- **CARDIAC WORKUP**—ECG, Holter monitor if suspect arrhythmia
- **SEIZURES WORKUP**—EEG
- **NEUROLOGIC WORKUP**—EMG/NCS if significant weakness thought to be related to peripheral lesion

MANAGEMENT

PREVENTION—education (proper shoes with thin soles, avoid hot tubs, drink 1.5–2 L/day, getting up slowly). **Exercise** (balance and gait training, muscle strengthening, day programs). **Environmental assessment** (remove loose rugs, non-slip bath mats, lighting, stair rails). **Tapering and discontinuation of medications**, if appropriate. **Referral** (physiotherapy, occupational therapy, ophthalmology, geriatrics, cardiology if appropriate). **Treatment and prevention of osteoporosis** (see OSTEOPOROSIS p. 403)

Osteoporosis

See OSTEOPOROSIS (p. 403)

Urinary Incontinence

CMAJ 1997 157:8; NEJM 2008 358:10

DIFFERENTIAL DIAGNOSIS OF CHRONIC URINARY INCONTINENCE

URGE (most common. Sudden, uncontrollable. Associated with urinary frequency and nocturia)

- **IDIOPATHIC**
- **NEUROLOGIC/DETRUSOR HYPERREFLEXIA**—normal pressure hydrocephalus, dementia, stroke
- **GU BLADDER/DETRUSOR INSTABILITY**—infection, stone, tumor, inflammation

STRESS (small volumes with ↑ abdominal pressure, e.g. coughing, sneezing, laughing)

- **URETHRAL HYPERMOBILITY**—childbirth, menopausal
- **SPHINCTER WEAKNESS**—post-TURP

OVERFLOW (over-distended bladder, small volumes but continuous leakage, incomplete emptying)

- **BLADDER OUTLET OBSTRUCTION**—BPH, prostate cancer
- **URETHRAL/BLADDER NECK STRICTURE**
- **DETRUSOR HYPOCONTRACTILITY**—peripheral neuropathy, alcohol, herniated disc, spinal stenosis, fibrotic detrusor

MIXED/DETRUSOR HYPERACTIVITY WITH IMPAIRED CONTRACTILITY (DHIC)—combines symptoms of urge and overflow incontinence with frequency and large volume, usually late stages of above (e.g. BPH or diabetes mellitus)

DIFFERENTIAL DIAGNOSIS OF CHRONIC URINARY INCONTINENCE (CONT'D)

FUNCTIONAL (reduced mobility, inability to ambulate to toilet)

DIFFERENTIAL DIAGNOSIS OF TRANSIENT URINARY INCONTINENCE

★DIAPERS★
DELIRIUM
INFECTION—symptomatic UTI
ATROPHIC VAGINITIS/URETHRITIS
PROSTATE
PHARMACY—diuretics, benzodiazepines, alcohol
PSYCHOLOGICAL
ENDOCRINE—hypercalcemia, diabetes mellitus, diabetes insipidus
RESTRICTED MOBILITY
STOOL IMPACTION

PATHOPHYSIOLOGY

PHYSIOLOGY OF URINATION

- **DETRUSOR MUSCLES**—parasympathetic S234 (contract), β2 sympathetic T10-L2 (relax)
- **INTERNAL SPHINCTER**—*α*1 sympathetic T10-L2 (contract)
- **EXTERNAL SPHINCTER**—somatic S234 (contract)

RATIONAL CLINICAL EXAMINATION SERIES: WHAT TYPE OF URINARY INCONTINENCE DOES THIS WOMAN HAVE?

	LR+	LR–
Stress incontinence		
Simple question: "Do you lose urine during sudden physical exertion, lifting, coughing or sneezing?"	2.2	0.39
Filled bladder stress test (fill bladder with 200 cc of saline, supine, and observe while cough)	9.4	0.07
Systematic assessment	3.7	0.20
Urge incontinence		
"Do you experience such a strong and sudden urge to void that you leak before reaching the toilet?"	4.2	0.48

APPROACH—"a systematic approach that includes a history, physical examination, and stress test increases the likelihood of correctly classifying the type of incontinence. The most helpful component of the assessment for determining the presence of urge incontinence is a history of urine loss associated with urinary urgency. A filled bladder stress test may be helpful for diagnosing stress incontinence. For primary care physicians unable to perform stress tests in their office, it would be reasonable to refer patients for further evaluation when a diagnosis is needed with more certainty. Measurement of the post-void residual urine volume detects incomplete bladder emptying, but no data support using this in women for separating out incontinence type"

JAMA 2008 299:12

INVESTIGATIONS

BASIC
- **LABS**—lytes, urea, Cr, glucose, Ca, urinalysis
- **MICROBIOLOGY**—urine C&S

SPECIAL
- **URODYNAMIC STUDIES**

MANAGEMENT OF CHRONIC URINARY INCONTINENCE

GENERAL MEASURES
- **ABSORPTIVE PADS**—incontinence pad or adult diapers (Depends®)
- **CATHETERIZATION/DIAPERS**—indwelling catheter, condom catheter, timed collection, intermittent self-catheterization

URGE INCONTINENCE—**behavioral modification, anticholinergic** (↓ detrusor contraction, ↑ bladder volume; *oxybutynin* 2.5–5 mg PO BID–TID or *XL* 5–30 mg PO daily; *tolterodine* 1–2 mg PO BID or *LA* 2–4 mg PO daily). **TCA** (*imipramine* 25–100 mg PO qhs; associated with significant adverse effects, particularly in the elderly)

STRESS INCONTINENCE—**bladder** training (30–50 pelvic floor exercises/day). **Weight loss** if obesity. **SSRI** (duloxetine hydrochloride). **Intravaginal pessaries/tampons** to exert pressure to provide urethral support. **Estrogen** (if concurrent vaginal atrophy)

OVERFLOW INCONTINENCE—**α1-antagonist** (only if BPH; *tamsulosin* 0.4–0.8 mg PO daily; *terazosin* 1–10 mg PO qhs; *doxazosin* 1–5 mg PO qhs). **5α reductase inhibitor** (only if BPH; *finasteride* 5 mg PO daily)

OVERFLOW WITH NEUROGENIC BLADDER—**acetylcholine agonist** (↑ bladder contractility; *bethanechol* 10–30 mg PO BID–QID for short term only, may require clean intermittent catheterization)

RESTRICTED MOBILITY—bedside urinal/commode, call bell, prompted voiding

Hearing Impairment

See HEARING IMPAIRMENT (p. 359)

Pharmacological Issues in the Elderly

Lancet 2007 370:9582; BMJ 2008 336:7644

PRINCIPLES OF DRUG USE IN THE ELDERLY

PRINCIPLES OF PHARMACOLOGY—elderly are at increased risk of adverse drug reactions because of altered physiology of aging, multiple co-existing illnesses, reduced homeostatic reserve, polypharmacy, and medical error. Of the

PRINCIPLES OF DRUG USE IN THE ELDERLY (CONT'D)

4 key components of pharmacokinetics (absorption, distribution, metabolism, excretion), only the last 3 are meaningfully affected by age. Pharmacokinetic changes are related to decreased

PRINCIPLES OF DRUG USE IN THE ELDERLY (CONT'D)

renal (most important) and hepatic function (phase I reactions ↓, phase II reactions unaffected), decreased lean body mass (↑ fat), decreased total body water, and increased total body fat

COMPLICATIONS—falls, delirium, incontinence, renal impairment, heart failure, gastrointestinal hemorrhage, hypoglycemia, drug–drug interactions

PRESCRIBING PRINCIPLES—initiate most medications at half usual starting dose, increase dose slowly. Carry out regular medication reviews and stop any unnecessary medications. Avoid medications with known significant side effects in the elderly. Avoid treating adverse drug reactions with further drugs

UNDER-PRESCRIBING IN THE ELDERLY

REASONS FOR UNDER-PRESCRIBING—under-recognition of medication benefit in older patients, affordability, and dose availability (i.e. requiring a dose of medication that is smaller than supplied by the manufacturer, resulting in more complicated dosing strategies such as once every other day dosing)

OVER-PRESCRIBING IN THE ELDERLY

POLYPHARMACY AND DRUG INTERACTIONS—57% of elderly use >5 drugs per week, 19% use >10 drugs per week; 1 in 25 are at risk for major drug–drug interaction, nearly half involve use of anticoagulants or antiplatelet agents

OVER-PRESCRIBING IN THE ELDERLY (CONT'D)

BEERS LIST 2012 (JAGS 2012 60:4)—list of designated drugs that fall in one of three categories: 1) should **always** be avoided (e.g. barbiturates); 2) drugs that are potentially inappropriate (e.g. glyburide), and 3) drugs that should be used with caution (e.g. SSRIs). Several deficiencies in the Beers criteria have been noted including potential drug-drug interactions and prescribing-omission errors. The STOPP (Screening Tool of Older Persons' Prescriptions) and START (Screening Tool to Alert to Right Treatment) were consequently developed. These criteria are organized by physiological systems

SUPPLEMENTS—49% of elderly use herbal or dietary supplements and are at increased risk of herb–drug interaction (e.g. ginkgo biloba and warfarin resulting in increased bleeding risk)

AVOID TREATING ADVERSE DRUG REACTIONS WITH FURTHER DRUGS—medications are often inappropriately prescribed to symptomatically treat side effect of another medication. For example, metoclopramide → extrapyramidal effects → levodopa. Metoclopramide users are >3 times more likely to be prescribed levodopa compared to non-users, a treatment generally reserved for management of idiopathic Parkinson's disease

COMMON ADVERSE DRUG REACTIONS AND DRUG–DRUG INTERACTIONS

CHARACTERISTIC SIDE EFFECTS OF DRUGS FREQUENTLY USED IN THE ELDERLY

Drugs	Adverse effects
α1 blockers (doxazosin)	Falls, orthostatic hypotension, dry mouth
Anticholinergics (diphenhydramine)	Delirium, urinary retention, constipation, dry mouth, blurred vision, postural hypotension
Benzodiazepines (lorazepam)	Falls, confusion
NSAIDs (indomethacin)	Gastrointestinal irritation and hemorrhage, renal impairment, hypertension, heart failure
Sulfonylureas (chlorpropamide)	Hypoglycemia
Tricyclic antidepressants (amitriptyline)	Falls, orthostatic hypotension, sedation, delirium, arrhythmias

COMMON ADVERSE DRUG REACTIONS AND DRUG–DRUG INTERACTIONS

WARFARIN INTERACTIONS—many medications implicated in increasing bleeding risk (↑ INR) with warfarin. Most severe interactions described with trimethoprim–sulfamethoxazole, erythromycin, amiodarone, propafenone, ketoconazole, fluconazole, itraconazole, metronidazole. Antibiotics, acetaminophen, steroids, and ginkgo biloba may also increase bleeding risk

COMMON ADVERSE DRUG REACTIONS AND DRUG–DRUG INTERACTIONS (CONT'D)

GRAPEFRUIT JUICE INTERACTIONS—grapefruit interferes with drugs that are metabolized by CYP3A4, including statins (simvastatin/lovastatin > atorvastatin), calcium channel blockers, and benzodiazepines

HEART FAILURE PRECIPITANTS AND EXACERBANTS—NSAIDs (>2 times risk for admission for HF, correlating with dose of drug), thiazolidinediones, sodium polystyrene sulfonate

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PALLIATIVE CARE

David Hui

Palliative Care-Specific Issues

INTRODUCTION

DEFINITION OF PALLIATIVE CARE—according to the World Health Organization, palliative care is "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual… Palliative care is applicable *early* in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications"

DEFINITION OF END-OF-LIFE—6 months or less of life expectancy

DEFINITION OF TERMINALLY ILL—6 months or less of life expectancy

RELIEF OF SUFFERING—suffering is defined as "the state of severe distress associated with events that threaten the intactness of the person." Living with advanced disease inevitably involves variable degrees of physical, psychosocial, and existential suffering. Palliative care aims at alleviating this suffering through the provision of

INTRODUCTION (CONT'D)

interdisciplinary comprehensive care from the time of diagnosis to the end-of-life

REFERRAL TO PALLIATIVE CARE—while palliative care is commonly associated with end-of-life care, it is most effective when incorporated *early* in the disease trajectory of life-limiting illnesses. Timely incorporation of palliative care principles can help to optimize symptom management, improve psychosocial interventions, enhance coordination of care, and facilitate patients' transition from active treatment to end-of-life care. Thus, patients living with incurable life-threatening conditions, such as advanced cancer, COPD, end-stage cardiac failure, stage V chronic kidney disease, progressive liver failure, and AIDS would benefit from palliative care involvement

SYMPTOM COMPLEX AND ASSESSMENT

SYMPTOM COMPLEX—patients with advanced disease typically experience multiple symptoms at the same time. In addition to underlying disease and associated symptom burden, expression of symptoms is modulated by patients' psychosocial and existential distress, cultural background, personality, past experiences, and comorbidities

SYMPTOM PREVALENCE IN TERMINALLY ILL PATIENTS

Symptom	Cancer (%)	AIDS (%)	Heart failure (%)	COPD (%)	CKD (%)
Pain	35–96	63–80	41–77	34–77	47–50
Depression	3–77	10–82	9–36	37–71	5–61
Delirium	6–93	30–65	30–65	18–32	18–33
Fatigue	32–90	54–85	69–82	68–80	73–87
Dyspnea	10–70	11–62	60–88	90–95	11–62
Anorexia	30–92	57	21–41	35–67	25–64

JPSM 2006 31:1

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DOI 10.1007/978-3-319-11821-5_14, © Springer International Publishing Switzerland 2016

SYMPTOM COMPLEX AND ASSESSMENT (CONT'D)

COMPREHENSIVE PALLIATIVE CARE ASSESSMENT—given the intricate nature of interaction between physical, psychosocial, and existential, it is important to perform regular screening to accurately assess and manage symptoms

- **SYMPTOM BATTERY**—Edmonton Symptom Assessment Scale (ESAS, Likert scale of 1–10 for 10 symptoms including pain, fatigue, nausea, depression, anxiety, drowsiness, appetite, well-being, shortness of breath, and sleep), Memorial Symptom Assessment Scale (MSAS), Palliative Care Outcome Scale (POS)
- **PAIN**—Edmonton Pain Classification System
- **DELIRIUM**—Mini-Mental State Examination, Memorial Delirium Assessment Scale
- **CAGE**—history of substance use (ever) may guide opioid therapy, potential marker of psychosocial distress
- **FUNCTION**—ECOG performance status, Karnofsky performance scale (KPS), and palliative performance scale (PPS). Performance status has prognostic utility and is one of the key factors in decision making at the end of life (e.g., discharge location, initiation or termination of treatment)

DEPRESSION IN THE PALLIATIVE SETTING

DIAGNOSIS—**somatic symptoms** (anorexia, fatigue, insomnia, weight loss) are less useful for diagnosis of depression since they are common in patients with advanced cancer. The diagnosis of depression depends on **psychological symptoms** (worthlessness, guilt, anhedonia, hopelessness, decreased will to live and suicidal ideation) for at least 2 weeks. Rule out hypothyroidism, hypercalcemia, hypoactive delirium, and medication side effects

TREATMENTS—**expressive/supportive counseling, cognitive behavioural therapy**, **antidepressants** (*mirtazapine* 15–45 mg PO qhs, *paroxetine* 10–20 mg PO daily, *fluoxetine* 10–20 mg PO daily, *sertraline* 25–100 mg PO daily, *fluvoxamine* 50–200 mg PO daily, *escitalopram* 10 mg PO daily), **psychostimulants** (*methylphenidate* 5–10 mg PO daily, dextroamphetamine, pemoline)

CARE FOR CAREGIVERS

EMPHASIS ON CAREGIVERS—palliative care is unique among medical disciplines in placing a particular emphasis on the well-being of patients' caregivers. This is because caregivers play a crucial role caring for their loved ones both physically and emotionally, and their well-being is often one of the key concerns for patients. Caregivers are at risk of developing psychosocial distress themselves, given the physical burden of providing care and the emotional burden of seeing their loved ones suffer. Moreover, many patients develop delirium close to the end of life, necessitating substitute decision making

CARE FOR CAREGIVERS (CONT'D)

INTERVENTIONS FOR CAREGIVERS—specific interventions may include (1) educating caregivers regarding signs and symptoms of dying so they can be more prepared, (2) supportive-expressive counseling for family members during split visits, (3) family meetings to help update all parties involved and to define goals of care, (4) bereavement counseling and support groups

COMMUNICATION IN THE PALLIATIVE SETTING

Patients and their families need to have a sound understanding of their disease, treatment options, and prognosis to make decisions. The section on "Communication Issues" (p. 451) covers a number of basic techniques in breaking bad news. For further information, readers are referred to a recent review that covers various communication topics related to the end-of-life, including discussion of diagnosis, prognosis, treatment decisions, advance care planning, transition of care, and preparing for death and dying

Cancer 2008 113:7

DECISION MAKING IN THE PALLIATIVE SETTING

Patients with advanced disease have to face many difficult decisions which are not only highly complex but also emotionally charged. One of the key roles of palliative care is to guide patients through the maze of difficult choices by providing individualized recommendations, taking into account the patient's preferences, health state, treatment options, and resources

MEDICAL DECISIONS AT THE END-OF-LIFE—initiation or discontinuation of treatments (e.g., chemotherapy, supplemental nutrition, life support), resuscitation orders (in-hospital, out-of-hospital), hospice referral (prognosis of 6 months or less and willingness to forgo life-sustaining treatments)

PERSONAL DECISIONS AT THE END-OF-LIFE—living arrangements as disease progresses (e.g., home, hospital, hospice; if home, may need

DECISION MAKING IN THE PALLIATIVE SETTING (CONT'D)

to consider family support, hired help, and/or home care, to arrange hospital bed at home and to ensure bathroom safety), personal directive, power of attorney, saying "good bye" to loved ones, completing specific tasks, will, funeral arrangements, care of family after death (especially children)

SPIRITUALITY IN THE PALLIATIVE SETTING

DEFINITION—relationship with oneself, with others (family, friends), and with God

SPIRITUAL NEEDS OF THE DYING

- **SEARCH FOR MEANING OF LIFE**—provide time for personal reflection, reminiscing, and life review
- **TO DIE APPROPRIATELY**—allow for interpretation of death, explore beliefs about pain and suffering
- **TO FIND HOPE THAT EXTENDS BEYOND THE GRAVE**—explore religious or other belief systems in order to give the reassurance of immortality, religious ritual

FACILITATION—listen, acknowledge, explore, reflect, integrate

SPIRITUAL HISTORY ★SPIRIT★

- **S**piritual belief system
- **P**ersonal spirituality
- **I**ntegration with a spiritual community
- **R**itualized practices/restrictions
- **I**mplications for medical care
- **T**erminal events planning

PITFALLS—AVOID trying to solve patient's problems or resolving unanswerable questions, going beyond a physician's expertise and role, imposing own religious beliefs, providing premature reassurance

RESOURCES—caregivers, spiritual counselors, chaplains, faith community

JAMA 2006 296:11

DIAGNOSIS OF IMPENDING DEATH

CHALLENGE—clinicians usually reluctant to make the diagnosis if any hope of improvement exists, particularly if no definitive diagnosis has been established. When recovery is uncertain, it is better to discuss this with patient and family. It is important to understand that the diagnosis of impending death can be made, knowing that there may still be a small chance of prolonged survival in some patients

DIAGNOSIS OF IMPENDING DEATH (CONT'D)

TELL-TALE SIGNS OF IMPENDING DEATH

- **EARLY SIGNS**—these signs are more common compared to late signs, are often observed >3 days before patients die, and have a moderate sensitivity/specificity for impending death. They include poor performance status (being bed bound), decreased level of consciousness, delirium and dysphagia
- **LATE SIGNS**—these signs are less common compared to early signs, mostly occur within the last 3 days of life, and have a very high specificity (>95%) and positive likelihood ratio (~10) for impending death within 3 days. They include the following
  - Neuromuscular changes—inability to close eyelids, non-reactive pupils, drooping of nasolabial fold, hyperextension of neck, death rattle, grunting of vocal cords
  - Neurocognitive changes—decreased response to verbal/visual stimuli, respiration with mandibular movement, Cheyne-Stokes breathing
  - Cardiovascular changes—pulselessness of radial artery, peripheral cyanosis and decreased urine output
- **APPLICATION**—absence of early signs are useful to rule out impending death, while presence of late signs are useful to rule in impending death

MEDICATION ADMINISTRATION IN THE PALLIATIVE SETTING

SUBCUTANEOUS ROUTE—preferred over intravenous route because it is associated with greater comfort, fewer complications, less maintenance, and medications can be given at home. Indwelling subcutaneous catheter may be used for convenience and patient comfort. Disadvantages include less rapid onset of medication effects. This route may not be suitable for certain medications

HYDRATION—hypodermoclysis rate is typically 1–2 mL/min per needle site. Contraindicated if severe edema, severe bleeding disorder, or severe thrombocytopenia

Principles of Pain Control

TYPES OF PAIN

NOCICEPTIVE PAIN—**somatic** (musculoskeletal pain, fractures, arthritis, bone metastases), **visceral** (obstruction, liver metastases)
NEUROPATHIC PAIN—**dysesthetic** (constant burning), **neuralgic/lancinating** (paroxysms of shooting pain)
PSYCHOSOCIAL PAIN

PATHOPHYSIOLOGY

DEFINITION OF PAIN—an unpleasant sensory and emotional experience associated with actual or potential tissue injury or described in terms of such damage. The concept of total pain is the sum of all physical, emotional, psychosocial, and spiritual pain

PREVALENCE OF CANCER PAIN—about 80% experience some form of pain during their course of illness; 80% due to tumor; 20% due to cancer therapy, and >5% due to other unrelated diseases

TOLERANCE—normal pharmacophysiological effect in which increasing doses of opioids are required to provide the same analgesic effect over time

PATHOPHYSIOLOGY (CONT'D)

DEPENDENCE—normal pharmacophysiological effect with the development of withdrawal symptoms (e.g., agitation, pain, fever, sweats, tremor, tachycardia) if opioid is stopped abruptly after a prolonged period of use. In general, a minimum of one-third of total daily opioid dose is required to prevent withdrawal symptoms

ADDICTION—abnormal psychopathological compulsion to use a substance affecting daily function. Although the majority of patients using analgesics as prescribed will not get addicted and should be reassured, approximately 10–20% of patients (with a history of substance use, CAGE positive) are at risk of developing opioid dependence/addiction. These individuals may be prescribed an ever escalating dose of opioid, without adequate pain control. These patients need to be monitored more frequently, have random urine drug screening, education, and careful titration of analgesics to optimize their function

CAUSES OF INTRACTABLE CANCER PAIN—disease progression, neuropathic pain, bone pain, breakthrough pain, delirium, substance use, depression/anxiety, and somatization (i.e., psychosocial/existential distress)

DISTINGUISHING FEATURES OF PAIN

	Somatic	Visceral	Neuropathic
Location	Localized	Poorly localized, referred	Radiation, dermatome
Nature	Aches	Squeezing, cramping	Shooting, burning
Analgesics	Opioids, NSAIDs	Opioids	Opioids, TCAs, antiepileptics, venlafaxine

MANAGEMENT

FIRST LINE (non-opioids)—*acetaminophen* 650 mg PO q4h, NSAIDs (*ibuprofen* 300–800 mg PO TID–QID) may be particularly useful for bone metastases, hypertrophic pulmonary osteoarthropathy, soft tissue infiltration, arthritis, serositis, and postoperative pain. Consider ceiling dose effect. Common side effects include gastritis, peptic ulceration, hypertension, fluid retention,

MANAGEMENT (CONT'D)

renal dysfunction (pre-renal, AIN), impaired platelet function. COX-2 inhibitors are associated with decreased risk of gastric ulceration and platelet dysfunction, but potentially higher risk of cardiovascular events

SECOND LINE (weak opioids)—*codeine* 30–60 mg PO q4h, *acetaminophen/codeine* 325 mg/30 mg 1–2 tabs PO q4h, *acetaminophen/*

MANAGEMENT (CONT'D)

hydrocodone 325 mg/5–10 mg PO q4h, *tramadol* 50–100 mg PO q4–6 h

THIRD LINE (strong opioids)—*morphine* 5 mg PO q4h and 2.5 mg q1h PRN, *hydromorphone* 2 mg PO q4h and 1 mg q1h PRN, *oxycodone* 5 mg PO q4h and 2.5 mg q1h PRN, fentanyl (only if pain stable), methadone

PROCEDURES—surgical interventions (celiac plexus/splanchnic block, subarachnoid block, cordotomy, epidural/intrathecal infusion, vertebroplasty) may be added to any line as needed

ADJUVANT THERAPIES

- **MEDICATIONS MITIGATING ADVERSE EFFECTS OF OPIOIDS**—start bowel protocol (*senna* 2 tab PO qhs) and anti-nausea (*metoclopramide* 10 mg PO q4h) at the same time of opioids. *Methylphenidate* 5–10 mg PO qAM and 5–10 mg q noon may be used for opioid sedation
- **TRICYCLIC ANTIDEPRESSANTS** (neuropathic pain)—*nortriptyline* 25 mg PO qhs initially, increase by 25 mg/day every week if tolerated, target 75 mg PO qhs-BID
- **ANTICONVULSANTS** (neuropathic pain, opioid-induced myoclonus)—*gabapentin* 100–300 mg PO TID, *pregabalin* 100 mg PO TID, *carbamazepine* 100 mg PO BID, *phenytoin* 100 mg PO TID
- **ANTISPASMODICS**—*baclofen* 10 mg PO TID muscle for spasms
- **ANTINEOPLASTIC TREATMENTS** (cancer pain)—chemotherapy, radiation (external beam radiation for focal tumor infiltration, Strontium[89], or Samarium[153] for multifocal osteoblastic bone metastases), hormonal agents
- **BISPHOSPHONATES** (bone metastases, hypercalcemia)—*pamidronate* 60–90 mg in 500 mL NS IV over 4–6 h, *zoledronate* 4 mg IV
- **CORTICOSTEROIDS** (acute nerve/spinal cord compression, visceral distension, increased intracranial pressure, and soft tissue infiltration)—*dexamethasone* 8–10 mg PO BID

OTHERS—physical therapy (massage, acupuncture, trigger point injection), psychological therapy (relaxation, imagery, biofeedback)

TREATMENT ISSUES

OPIOID USE

- **STARTING DOSE**—start with short-acting opioids, which are usually given q4h around the clock, with breakthroughs (10–20% of total daily dose) given q1–2 h (see table below). May need to increase scheduled dose if ≥3 breakthroughs/day
- **ROUTE**—for regular opioids, PO is preferred over SC/IV. IV/SC dose = ½ of PO dose for most opioids
- **MAXIMUM DOSE**—there is no absolute number for the ceiling dose of opioids that can be given. This is only limited by opioid toxicity
- **MAINTENANCE**—if patient on stable dose of opioids, may consider switching to slow release (SR) formulations or fentanyl patch for convenience and improved compliance. Long-acting opioids provide similar pain control as short-acting opioids
- **TITRATING DOWN**—if patient did not require any rescue opioids and pain is well controlled, consider decreasing regular dose by 25–50% every 1–7 days to optimally control pain with minimum opioid dose
- **CAUTIONS**—avoid meperidine because of high toxicity from metabolites. Avoid fentanyl patch for unstable pain (although fentanyl infusion can be useful)

OPIOID TOXICITY

- **ADVERSE EFFECTS**—common side effects include nausea, somnolence, dry mouth, pruritus, and constipation. While these side effects generally resolve within a few days, patients do not develop tolerance to constipation and would require laxatives throughout opioid treatment. Patients receiving high doses of opioids may develop neurotoxicity, which include myoclonus, hyperalgesia, delirium, hallucinations, cognitive impairment, and respiratory depression. Long-term side effects include secondary adrenal insufficiency, hypogonadism, sexual dysfunction, osteoporosis, immunosuppression, altered renal function, and peripheral edema. Methadone is also associated with QT prolongation at high doses

TREATMENT ISSUES (CONT'D)

- **TREATMENT OF OPIOID TOXICITIES**—ensure adequate hydration, opioid rotation, exclude underlying aggravating metabolic factors (uremia, liver failure, hypercalcemia), and symptom management (e.g., treat nausea and constipation)

TREATMENT ISSUES (CONT'D)

OPIOID ROTATION—common reasons for rotation include opioid induced neurotoxicities (sedation, nightmares, hallucinations, myoclonus), poor analgesic response despite high opioid doses, and logistical factors (e.g., loss of oral route, cost considerations). Remember to dose reduce by 25–50% to account for tolerance

EQUIANALGESIC TABLE

	Ratio[a]	Starting	q1–2 h PRN	Route
Codeine[b]	0.1	30–60 mg q4h PRN	–	PO/PR
Hydrocodone[c]	1	5–10 mg q4h PRN	–	PO
Morphine	1	5 mg q4h	2.5–5 mg	PO/PR/SC/IV
Hydromorphone	5	1–2 mg q4h	0.5–1 mg	PO/PR/SC/IV
Oxymorphone	3	5 mg q8h	2.5 mg	PO
Oxycodone[d]	1.5	5 mg q4h	2.5 mg	PO/PR/SC
Fentanyl drip	100	10–50 μg/h	25 μg	IV
Methadone	2–20[e]	5 mg q8–12 h	–	PO/PR/IV

[a]Higher number indicates greater potency
[b]Tylenol #1–3 = acetaminophen plus codeine with or without caffeine
[c]Vicodin, Lortab, Norco = acetaminophen plus hydrocodone
[d]Percocet = acetaminophen plus oxycodone
[e]See methadone conversion table below

TREATMENT ISSUES (CONT'D)

FENTANYL DURAGESIC CONVERSION

Fentanyl TD (μg/h)	Morphine PO (mg)
25	45–134
50	135–224
75	225–314
100	315–404
125	405–494
150	495–584

- **CONVERSION BETWEEN FENTANYL PATCH (IN μG/H) AND ORAL MORPHINE (IN MG/DAY)**—consider using a ratio of 3.6, e.g., fentanyl patch of 25 μg/h is equivalent to 25 × 3.6 = 90 mg of oral morphine/day
- **CONVERSION BETWEEN INTRAVENOUS FENTANYL AND INTRAVENOUS MORPHINE**—consider using a ratio of 10 μg: 1 mg

TREATMENT ISSUES (CONT'D)

- **BIOAVAILABILITY OF FENTANYL IS HIGHLY VARIABLE**—transdermal 90%, sublingual 65%, and transmucosal (lozenge) 50%

METHADONE CONVERSION

1. **DETERMINE THE DOSE EQUIVALENT**

Oral morphine equivalent daily dose (mg/day)	Initial dose ratio (morphine: methadone)
<30	2:1
30–99	4:1
100–299	8:1
300–499	12:1
500–999	15:1
>1000	20:1 or greater

2. **DETERMINE THE SCHEDULE**

	Day 1	Day 2	Day 3	Day 4
Morphine (MS)				
	66%	33%	0%	0%
	TDD	TDD	TDD	TDD
Methadone (ME)				
	33%	66%	100%	100%
	TDD	TDD	TDD	TDD
Break through	10%	10%	10%	10%
	w/morphine	w/morphine	w/morphine	w/methadone

TDD total daily dose, breakthrough dose is 10% of TDD. Methadone is usually given q12h, sometimes q8h. Start low and go slow is the key for using methadone. Pay close attention to sedation during methadone conversion and be prepared to reduce dose if necessary. To improve tolerability with conversion, consider spreading out to a dose change every 3 days instead of everyday. Due to its complex pharmacology, methadone should only be prescribed by clinicians familiar with this drug

TREATMENT ISSUES (CONT'D)

PROGNOSTIC FACTORS FOR POOR PAIN CONTROL—somatization, substance use, cognitive impairment, neuropathic pain

SPECIFIC SITUATIONS

- **RENAL FAILURE**—methadone is hepatically excreted and not dialyzable. Thus, methadone is the drug of choice for patients with renal failure and/or on dialysis. Other opioids for patients with renal failure include fentanyl (excreted unchanged by the kidneys with no intermediate metabolites) and hydromorphone (more potent and thus fewer toxic metabolites)
- **NEUROPATHIC PAIN**—opioids are effective against neuropathic pain. Methadone is theoretically more useful because of its NMDA antagonist activity. Also consider use of non-opioids such as gabapentin, pregabalin, carbamazepine, venlafaxine, and TCAs

TREATMENT ISSUES (CONT'D)

Delirium

See DELIRIUM (p. 432)

Cancer-Related Fatigue

CAUSES

ALTERED PHYSIOLOGY—cytokine dysregulation, serotonin neurotransmitter dysregulation, HPA axis dysfunction, circadian rhythm disruption, vagal afferent activation, alterations in muscle ATP metabolism

CONTRIBUTING FACTORS ★ASTHENIC★

- **ANEMIA, ANOREXIA**
- **SLEEP DISTURBANCES, SHORTNESS OF BREATH**
- **THROBBING PAIN**
- **HEAD**—depression, anxiety
- **ELECTROLYTES**—Na, K, Mg, Ca
- **NUTRITIONAL FAILURE**—anorexia–cachexia
- **INACTIVITY**
- **COMORBIDITIES**—cardiac/pulmonary failure, hepatic/renal failure, neurologic/endocrine failure (hypothyroidism, hypogonadism, adrenal insufficiency), infections

PATHOPHYSIOLOGY

DEFINITION—a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that interferes with usual functioning. Cancer-related fatigue is distinct from everyday tiredness as it does not correspond to the patient's level of exertion and is not typically relieved by rest or sleep. Note that fatigue has not been well studied in other palliative care settings, although the underlying pathophysiology and treatments are similar to cancer-related fatigue

PREVALENCE—cancer-related fatigue is essentially present throughout the cancer journey, including 40% at diagnosis, 80–90% during cancer treatment, 30% 1-year post-treatment, 75% with metastatic disease, and >90% at the end of life. It is also underdiagnosed and under-treated

CLINICAL FEATURES

SCREENING—"How would you rate your fatigue on a scale of 0–10 over the past 7 days?"

0	Absence of fatigue
1–3	Mild fatigue
4–6	Moderate fatigue
7–10	Severe fatigue

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, TSH, Mg, Ca, albumin

MANAGEMENT

NON-PHARMACOLOGIC—aerobic or resistive exercise for at least 30 min/day (strongest evidence), psychosocial interventions, nutritional counseling, sleep therapy

PHARMACOLOGIC—*methylphenidate* 5 mg PO qAM and noon, and 5 mg q4h PO PRN, up to 20 mg/day; *modafinil* 200 mg PO daily, corticosteroids (*dexamethasone* 4 mg PO BID for 2 weeks)

Dyspnea in the Palliative Setting

DIFFERENTIAL DIAGNOSIS OF ACUTE DYSPNEA

RESPIRATORY

- **PARENCHYMA**—pneumonia, ARDS, lymphangitic carcinomatosis, lung cancer
- **AIRWAY**—COPD exacerbation, asthma exacerbation, acute bronchitis, bronchiectasis, obstruction (cancer)
- **VASCULAR**—pulmonary embolism, pulmonary hypertension, SVC obstruction
- **PLEURAL**—pleural effusion, pneumothorax

DIFFERENTIAL DIAGNOSIS OF ACUTE DYSPNEA (CONT'D)

CARDIAC

- **MYOCARDIAL**—HF exacerbation, myocardial infarction
- **VALVULAR**—aortic stenosis, acute aortic regurgitation, endocarditis
- **PERICARDIAL**—pericardial effusion, tamponade

SYSTEMIC—sepsis, metabolic acidosis, anemia

OTHERS—neuromuscular (cachexia), anxiety, tense ascites

PATHOPHYSIOLOGY

DEFINITION—a subjective experience of breathlessness related to patient's physical, mental, emotional, and social circumstances. Degree of dyspnea may not correlate with physical findings, such as tachypnea, wheezing, cyanosis, and O_2 saturation

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, D-dimer
- **MICROBIOLOGY**—sputum Gram stain/AFB/C&S
- **IMAGING**—CXR, CT angiogram, V/Q scan

SPECIAL

- **ECG**—if suspect ACS
- **ABG**—judicious use in the palliative care setting

MANAGEMENT

TREAT UNDERLYING CAUSE—palliative radiation and/or chemotherapy may be used in specific cases

NON-PHARMACOLOGICAL—fan blowing in face (particularly effective if add cool cloth to fan), open windows, relaxation techniques, distraction therapy

PHARMACOLOGICAL—supplemental **O2** if hypoxemic, **opioids** (similar for pain control, although the starting doses may be lower. If already on opioids, may increase dose by 25%. No difference shown between q4h dose and infusion), **corticosteroids** (*dexamethasone* 4–8 mg PO BID), **bronchodilators**, **diuretics** (furosemide SC if HF), **non-invasive positive pressure ventilation** (BiPAP) may be beneficial for patients with hypercapnia and/or significant respiratory muscle weakness, high flow oxygen (up to 60 L/min of humidified oxygen via nasal prongs) for patients with severe hypoxemia. **Palliative sedation** as a last resort

PROCEDURES—if significant pleural effusion, consider thoracentesis, pleurodesis, or indwelling pleural catheters

TREATMENT ISSUES

PALLIATIVE SEDATION

- **DEFINITION**—the use of medications to relieve intolerable suffering from refractory symptoms through sedation. Refractory symptoms are defined as those for which all possible treatment has failed or it is estimated that no methods are available for palliation within the time frame and the risk–benefit ratio that the patient can tolerate
- **INDICATIONS**—when suffering (delirium/agitation, dyspnea, pain) persists despite all other means; not to be confused with euthanasia. MUST ensure detail discussion with patient (if possible), family, and the interprofessional palliative care team prior to initiation of treatment with clear documentation
- **MEDICATIONS**—**benzodiazepines** (*midazolam* start at 1 mg/h IV/SC, titrate to achieve sedation, lorazepam), **neuroleptics** (e.g., haloperidol, chlorpromazine, methotrimeprazine [good for delirium and may be combined with midazolam]), **propofol** (intravenous access required, may be used temporarily)
- **ETHICS**—palliative sedation is permissible when the primary intention is relief of suffering, even if survival may be shortened (i.e., the doctrine of double effect). Systematic reviews showed that palliative sedation is not associated with shortened survival

SPECIFIC ENTITIES

DEATH RATTLE—due to patient's inability to clear upper respiratory secretions. Patient's family should be reassured that this does not indicate that the patient is dyspneic or in distress. Treatments to decrease respiratory secretions include re-positioning, Trendelenburg for a minute then general oropharyngeal suction, *glycopyrrolate* 0.2 mg SC q4–6 h or 0.4–1.2 mg/day SC/IV, or *hyoscine hydrobromide/scopolamine* 0.8 mg SC initially, then 0.2–0.6 mg SC q1h PRN, total 0.8–2 mg/day (note: *hyoscine hydrobromide/scopolamine* is frequently confused with hyoscine butylbromide/buscopan, which is used to relieve GI/bladder spasms and is dosed very differently)

BREATHING PATTERN CHANGES IN DYING PATIENTS—reassurance should be provided to the patient's family that breathing pattern changes described below are not associated with dyspnea as the patient is unconscious.

- **CHEYNE–STOKES BREATHING**—cyclic variation in rate and depth of breathing with apneic spells. Causes include bilateral cerebral damage, HF, uremia, drug-induced respiratory depression
- **KUSSMAUL BREATHING**—rapid, deep, and regular breathing. Causes include mid-brain and pontine infarction/hypoxia, exercise, anxiety, metabolic acidosis
- **ATAXIC BREATHING**—irregular breaths with long apneic periods caused by medullary damage

Nausea and Vomiting in the Palliative Setting

INVESTIGATIONS

BLOOD TESTS—CBCD, lytes, urea, Cr, glucose, Ca, Mg, PO_4, cortisol
URINE TESTS—urinalysis
MICROBIOLOGY—urine C&S
IMAGING—CXR, AXR (rule out bowel obstruction and constipation)

Related Topic
Nausea and Vomiting (p. 123)

MANAGEMENT

TREAT UNDERLYING CAUSE—bowel obstruction (decompression, octreotide), constipation (bowel regimen), opioid use (opioid rotation), hypercalcemia (hydration, bisphosphonates)

NAUSEA CONTROL

- **FIRST LINE** (D2 blockade)—*metoclopramide* 10 mg PO/SC/IV q4h and q1h PRN or *prochlorperazine* 10 mg PO/IV q4h and q1h PRN. Avoid if complete bowel obstruction
- **SECOND LINE** (more D2 blockade)—switch *metoclopramide* to IV/SC infusion 60–120 mg/day. Also consider adding *haloperidol* 1–2 mg IV/SC q8–12 h and q1h PRN
- **FURTHER OPTIONS**
- **H1 BLOCKADE**—*dimenhydrinate* 50 mg PO/SC/IV q4h or *diphenhydramine* 50 mg PO/SC/IV q4h
  - **STEROIDS**—*dexamethasone* 4–10 mg PO/SC/IV BID
  - **NEUROLEPTICS**—*methotrimeprazine* 5–25 mg PO TID, *chlorpromazine* 10–25 mg PO q4h
  - **CANNABINOID AGONISTS**—*nabilone* 1 mg PO daily may also be considered
  - **5HT3 ANTAGONISTS**—*ondansetron* 8 mg PO daily-TID for chemotherapy-induced nausea and vomiting

MANAGEMENT (CONT'D)

- **PROMOTILITY AGENTS**—*domperidone* 10 mg PO TID-QID, *cisapride* 10 mg PO TID–QID (special release)

SPECIFIC ENTITIES

BOWEL OBSTRUCTION IN THE PALLIATIVE SETTING

- **PATHOPHYSIOLOGY**—3% of all advanced cancers, particularly ovarian (11–42%), colorectal (5–24%), gastric, endometrial, prostate, and bladder. If inoperable, median survival is only 2 months
- **CAUSES**—**intraluminal** (mass, constipation, intussusception), **luminal** (carcinomatosis causing dysmotility, bowel infarction), and **extraluminal** (compression, adhesions)
- **CLINICAL FEATURES**—nausea and vomiting, abdominal distension and pain, obstipation, absent bowel sounds
- **DIAGNOSIS**—AXR or CT abdomen
- **MANAGEMENT**
  - **SUPPORTIVE MEASURES**—intravenous fluids, bowel rest, pain control (opioids, hyoscine butylbromide/buscopan), antiemetics (*metoclopramide* 10 mg IV q4h if partial obstruction), NG suction (clump when output <100 cc/day and ensure no further N&V before removal). Consider venting PEG tube insertion
  - **ANTI-SPASMODIC/ANTISECRETORY AGENTS**—antimuscarinic agents (*hyoscine butylbromide/buscopan* 10–20 mg PO/IV/IM TID, atropine), somatostatin analogues (*octreotide* 10 µg/h IV or 50 µg SC q8h)
  - **BYPASS OBSTRUCTION**—surgery, colonic stent placement, venting gastrostomy, corticosteroids to decrease local inflammation

Constipation in the Palliative Setting

DIFFERENTIAL DIAGNOSIS

★DUODENUM★
DIET—low fiber, dehydration
ΨSYCHIATRY—depression, somatization, obsessive compulsive disorder
OBSTRUCTION—cancer, strictures, adhesions
DRUGS—opioids, TCAs, neuroleptics, antihistamines, calcium channel blockers, iron, antacids

DIFFERENTIAL DIAGNOSIS (CONT'D)

ENDOCRINE—diabetes, hypothyroidism, hypercalcemia, hypokalemia, hypomagnesemia, uremia
NEUROLOGIC—spinal cord compression/injury, Parkinson's, multiple sclerosis, stroke, autonomic neuropathy (cachexia–anorexia syndrome)
UNKNOWN/MISCELLANEOUS—immobility, irritable bowel syndrome (IBS), amyloidosis, scleroderma

PATHOPHYSIOLOGY

CONSTIPATION IN THE PALLIATIVE CARE SETTING—the most common causes are opioids, other medications, dehydration, and immobility. Even if there is no food intake, a small amount of stool is produced everyday due to shedding of intestinal epithelium. It is important to rule out bowel obstruction

RISK FACTORS FOR CONSTIPATION—old age, female sex, intraabdominal malignancies, opioids use

COMPLICATIONS OF CONSTIPATION—abdominal pain, distension, nausea and vomiting, overflow diarrhea, hemorrhoids, anal fissures, confusion/delirium, fear of opioid use

INVESTIGATIONS

BASIC

- **IMAGING**—AXR

SPECIAL

- **WORKUP**—lytes, urea, Cr, glucose, Mg, Ca, albumin, TSH

DIAGNOSTIC ISSUES

CONSTIPATION SCORE—based on flat abdominal X-ray. Divide into 4 quadrants (ascending, transverse, descending, and rectosigmoid colon). Rate amount of stool in each quadrant from 0 to 3. A total score >6/12 suggests constipation

Related Topic
Constipation (p. 141)

MANAGEMENT

PREVENTION IS KEY—a prescription for laxatives (e.g., *senna* 1–2 tabs PO qhs to start with) should *always* be given to the patient when starting an opioid

LIFESTYLE CHANGES—wheat **bran**, high-bran cereals, **exercise**, **hydration** (8–10 glasses/day)

SYMPTOM CONTROL

- **LAXATIVES**—in order of increasing potency: *senna* 1–4 tabs daily-QID, *milk of magnesia* 15–30 mL BID, *sorbitol* 15–30 mL daily-BID, *lactulose* 15–60 mL daily, *magnesium citrate* 150–300 mL daily, *bisacodyl/dulcolax suppositories* 1 PR PRN, *tap water enema* 500 mL PRN, *mineral oil enema* 100–250 mL PRN, p*olyethylene glycol* 17 g PO BID or *Golytely* 4 L PO/NG × 1 for severe constipation
- **μ-OPIOID RECEPTOR ANTAGONISTS**—indicated for patients with opioid-induced constipation despite at least 3 days of laxatives. *Methylnaltrexone* 12 mg SC × 1 day, repeat every other day as needed. These antagonists are peripheral acting, and thus do not affect pain control which happens centrally
- **MANUAL DISIMPACTION**—as last resort. For patients with spinal cord compression, it is important to use rectal measures (enemas, suppositories) as significant diarrhea/leakage could occur with oral medications alone

TREAT UNDERLYING CAUSE—stop potentially constipation-causing medications if possible

Anorexia–Cachexia

DIFFERENTIAL DIAGNOSIS

MALIGNANCY—**solid tumors** (primary, metastatic), **hematologic**

CHRONIC INFECTION—**atypical (TB), viral (HIV, HCV), fungal**, **parasitic**

CONNECTIVE TISSUE DISEASE—**seropositive** (RA, SLE, dermatomyositis, polymyositis), **seronegative**, **vasculitis**

OTHER CHRONIC DISEASES

- **PULMONARY**—COPD, bronchiectasis
- **CARDIAC**—HF
- **ENDOCRINE**—type 1 diabetes, Addison's

PATHOPHYSIOLOGY

CACHEXIA VS. STARVATION—cachexia is defined as accelerated loss of skeletal muscle (and to a smaller extent, adipose tissue) in the context of a chronic inflammatory response and excessive catabolism. The resulting weight loss cannot be adequately treated with aggressive feeding. In contrast, simple starvation is characterized by a loss of mostly adipose tissue and a caloric deficiency that can be reversed with appropriate feeding

CACHEXIA–ANOREXIA SYNDROME—due to a combination of pathophysiologic alterations

PATHOPHYSIOLOGY (CONT'D)

including chronic inflammation from cytokine release (e.g., TNF, IL-1, IL-6), dysregulated ATP–ubiquitin–proteasome pathway, lipid mobilizing factor (cancer), neuro-hormonal dysregulation such as elevated cortisol levels, ghrelin and insulin resistance, low serum testosterone, and sympathetic activation. These changes result in a constellation of signs/symptoms such as increased basal energy expenditure, cachexia, disproportionate and excessive loss of lean body mass (muscle loss >fat loss), anorexia, xerostomia, dysphagia (oropharyngeal due to mechanical reasons), nausea, fatigue, autonomic dysfunction, and decreased performance status

CONTRIBUTORS OF WEIGHT LOSS—in addition to an inflammatory catabolic process in primary cachexia, a number of associated symptoms may contribute to decreased appetite and weight loss (also known as secondary cachexia)

- **NAUSEA**—chemotherapy, bowel obstruction
- **MUCOSITIS**—chemotherapy, radiation
- **DENTAL ISSUES**—dentures, abscess
- **TASTE CHANGES**—medications, xerostomia
- **PAIN**—abdominal, other body sites
- **DYSPHAGIA**—oropharyngeal, esophageal
- **EARLY SATIETY**—autonomic neuropathy, opioid induced gastroparesis, ascites, hepatosplenomegaly
- **CONSTIPATION**—opioids, dehydration
- **DEPRESSION**

DIFFERENTIAL DIAGNOSIS

★ANOREXIA★
ACHES AND PAIN
NAUSEA AND VOMITING
ORAL CANDIDIASIS
REACTIVE DEPRESSION
EVACUATION—constipation
XEROSTOMIA—taste change
IATROGENIC—chemotherapy, radiation to esophagus
ILLNESS—underlying disease
ACID RELATED—GERD

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, Ca, PO_4, Mg, ESR, CRP, fasting glucose, TSH, AST, ALT, ALP, bilirubin, INR, albumin, fasting lipid profile, AM total testosterone level
- **BODY WEIGHT**—regular and frequent assessments
- **CALORIE COUNT**—determine daily intake

INVESTIGATIONS (CONT'D)

SPECIAL

- **BODY COMPOSITION AND METABOLISM STUDIES**—bone density scan, bioelectrical impedance, indirect calorimetry
- **MALIGNANCY WORKUP** (if no obvious cause for cachexia)—serum protein electrophoresis, PSA (if male), fecal immunochemical test or fecal occult blood, pap smear and pelvic examination, mammography, CXR
- **INFECTION WORKUP** (if no obvious cause for cachexia)—serologies (HBV, HCV, HIV, *Treponema pallidum*)
- **INFLAMMATORY WORKUP** (if no obvious cause for cachexia)—ANA, RF, C3, C4, p-ANCA, c-ANCA, cryoglobulins

MANAGEMENT

NUTRITIONAL COUNSELING—patients with advanced disease should be encouraged to eat things they enjoy in small and frequent portions, without have having to worry too much about their nutritional content. Dietician referral may be useful. Aggressive measures such as parenteral or enteral feeding have limited impact on survival but may significantly decrease the quality of life. Their use should be limited to patients for whom starvation is a major component of weight loss (e.g., dysphagia from esophageal or head and neck cancer, bowel obstruction from peritoneal carcinomatosis)

OREXIGENIC AGENTS (appetite stimulants)—**corticosteroids** (*dexamethasone* 4 mg PO daily, patients may experience an increase in appetite and sense of well-being. Weight gain may not occur and duration of appetite stimulation is often short. Risk of myopathy and other steroid associated side effects). **Progestational agents** (*megestrol acetate* 400–800 mg PO daily has been shown to improve weight and appetite, but not quality of life or survival. However, it is associated with increased thromboembolic risk, swelling, impotence, and GI upset). **Serotonin antagonists**

ANTICATABOLIC AGENTS (antimetabolic and anticytokine)—less effective than steroids and megestrol, and/or insufficient evidence

ANABOLIC AGENTS (primarily hormonal)—less effective and/or insufficient evidence

CANNABINOIDS—not helpful in cancer patients but may be useful in chronic inflammatory conditions such as HIV/AIDS

OTHER POTENTIAL AGENTS—melatonin, mirtazapine, thalidomide, lenalidomide are considered investigational at this time

MANAGEMENT (CONT'D)

TREATMENT OF CONTRIBUTORS—consider treatment of nausea with antiemetics, mucositis with lidocaine vicous 2% or lidocaine spray, taste changes with *zinc sulfate* 220 mg PO BID, early satiety with metoclopramide, pain with analgesics, constipation with laxatives, and depressive mood with antidepressants

TREATMENT ISSUES

MEGESTROL ACETATE VS. CORTICOSTEROIDS—megestrol has been shown to increase appetite and weight (but not lean body mass) and may be considered for intermediate–term use if weight loss is the predominant symptom. However, its significant side effect profile should be taken into consideration. Corticosteroids may be useful for short-term (i.e., days to weeks) use, particularly if other symptoms (e.g., pain, fatigue, nausea, dyspnea) are present. Long-term use of steroids should be avoided due to side effects

TREATMENT ISSUES (CONT'D)

Related Topics
Nausea and Vomiting (p. 123)
Supplemental Nutrition (p. 460)

Communication Issues

COMMUNICATION TECHNIQUES

1. **ASSESS PATIENT'S UNDERSTANDING** of their disease and their expectations before sharing information
2. **"ASK-TELL-ASK" APPROACH**—if information is sensitive, ask for patient's permission before starting, then share information tailored to their intellectual comprehension and emotional resilience and assess their need for further information before proceeding
3. **EMPATHIC RESPONSES**—acknowledge patient's emotion and facilitate its expression, using phrases such as "I can see this is a difficult time for you"
4. **ACTIVE LISTENING**—facilitate discussion by summarizing, use of appropriate pauses or phrases such as "Tell me more"
5. **NON-VERBAL COMMUNICATION**—pay attention to speech, posture, facial expression, appearance, and setting

BREAKING BAD NEWS: THE GENTLE ART OF TRUTH TELLING

★SPIKES★

SETTING—establish an appropriate setting for the discussion. Sit down and talk slowly with good eye contact. Get healthcare team and family members involved (if appropriate). Be aware of cultural and religious differences

BREAKING BAD NEWS: THE GENTLE ART OF TRUTH TELLING (CONT'D)

PERCEPTION: HOW MUCH DOES PATIENT KNOW?

- "What do you understand about your illness?"
- "What did the other doctors tell you?"
- "Are you worried about your illness?"
- "How do you think you are doing now?"

INFORMATION: HOW MUCH DOES PATIENT WANT TO KNOW? WARN AND PREPARE THE PATIENT

- "I have reviewed the tests and I'm afraid that I have some bad news for you."
- "We have some difficult matter to discuss. Do you feel ready for this discussion?"
- "Would you like me to tell you everything? Or would you prefer a more general overview?"
- "Some people like a whole lot of details, others do not. What would you prefer?"

KNOWLEDGE: DELIVER INFORMATION—discuss diagnosis, treatments, prognosis, and provide understanding of the natural history of disease. Pause frequently to check understanding. If delivering prognosis, discuss it in terms of "days," "weeks," "months", or "years" instead of quoting median survival numbers. Check patient's understanding frequently: "Any questions? Would you like me to continue?"

BREAKING BAD NEWS: THE GENTLE ART OF TRUTH TELLING (CONT'D)

EMOTIONS: EMPATHIC RESPONSE, NORMALIZE

- "This is a very difficult time for you and your family"
- "Many people feel frustrated and sad… Is this your experience?"
- "I'd like to check so I know where you're at"

STRATEGY: EMPOWER PATIENT AND PROVIDE FOLLOW-UP, SUPPORT RESOURCES, AND APPROPRIATE COUNSELING

- "There is a lot we can do even though there is no cure for your disease. We will keep our eyes open for new treatments and discuss them together"
- "I know this is very difficult news and a lot of information. It may be very difficult for you to think right now. I am available anytime if you have any questions"

Oncologist 2000 5:4

DISCUSSING RESUSCITATION STATUS

The following overview is based on JCO 2001 19:5, with a number of citations from the article

CONTEXT—establish an appropriate setting for the discussion. Sit down and talk slowly with good eye contact. Get healthcare team and family members involved (if appropriate)

WHAT DOES THE PATIENT UNDERSTAND?

- "What do you understand about your current health situation?"
- "Tell me about how you see your health"
- "What do you understand from what the doctors have told you?"

WHAT DOES THE PATIENT EXPECT?

- "What do you expect in the future?"
- "Have you ever thought about how you want things to be if you were much more ill?"
- "What are you hoping for?"

DISCUSS DNR ORDER, INCLUDING CONTEXT

- "If you should die despite all of our efforts, do you want us to use "heroic measures" to bring you back?"
- "How do you want things to be when you die?"
- "So, what you are saying is you want to be as comfortable as possible when the time comes"
- "What I hear you saying is you do not want us to 'call a code' if it would not do any good"

DISCUSSING RESUSCITATION STATUS (CONT'D)

- "What you have said is you want us to do everything we can to fight this cancer, but when the time comes, you want to die peacefully"
- "From what you have told me, I think it would be best if I put a DNR order on the chart"
- "Most patients who have expressed such opinions have a DNR order. I recommend that we put it on the chart"

RESPOND TO EMOTIONS

- "I can see this makes you sad"
- "Tell me more about how you are feeling"
- "You seem angry"

ESTABLISH AND IMPLEMENT A PLAN

- "We will continue maximal medical therapy. However, if you die despite everything, we would not use CPR to bring you back"
- "It sounds like we should move to a plan that maximizes your comfort. Therefore, in addition to a DNR order, I would like to ask my palliative care colleagues to come give you some information"
- Document clearly in the chart "In the event of cardiorespiratory arrest, no CPR/defibrillation/intubation/mechanical ventilation/inotropes/ICU/CCU"

WHAT IF PATIENT INSISTS ON FULL CODE STATUS DESPITE YOUR BELIEF THAT THIS WOULD CLEARLY CAUSE MORE HARM THAN GOOD?

- **ENSURE GOOD COMMUNICATION**—between all parties, establish trust, and try to understand patient's rationale. Do not rush—give the patient and family time to digest the information and respond emotionally
- **CONSIDER SOCIAL WORK CONSULT**—for family conference
- **ASK ABOUT RELIGION**—patients may want to involve pastoral care or their own spiritual support
- **CONSIDER BIOETHICIST CONSULT**
- **ASK FOR GUIDANCE FROM PATIENT**—"If someone is on life support, it becomes clear in a few days if they can recover or whether life support is prolonging an inevitable death. Please help us to determine what guidelines will be for deciding whether to remain on life support or not if you were not able to participate in the discussion at that time"

JCO 2001 19:5

Prognostication in Far Advanced Cancer Patients

REASONS FOR DISCUSSING PROGNOSIS

PATIENT AUTONOMY—patients have the right to know, cultural appropriateness

END-OF-LIFE PLANNING—important personal decisions influenced by time, time to express wishes (verbal, written), control of the situation/autonomy

CARE PLANNING—helps to avoid harm and discomfort by inappropriate therapies, initiation of medications (e.g., antidepressants), hospice admission

NOTE—advanced cancer is defined as locally advanced, metastatic or recurrent incurable cancer; far advanced cancer is defined as advanced cancer with a predicted survival of <3 months

PROGNOSTIC FACTORS

CLINICIAN PREDICTION OF SURVIVAL—clinician estimation of survival (generally 2–5× overestimation)

SYMPTOMS—poor performance status (median survival palliative performance scale 60–70% = 108 days, 30–50% = 41 days, 10–20% = 6 days), anorexia, cachexia, dysphagia, dyspnea, delirium

LABORATORY TESTS—elevated CRP, leukocytosis, lymphopenia, hypoalbuminemia, elevated LDH

OTHERS—cancer type and stage (less important in patients with far advanced cancer), comorbidities (less important if prognosis is poor. More useful in patients with longer expected survival such as those with prostate cancer)

PROGNOSTIC FACTORS (CONT'D)

Related Topics
Death and Dying (p. 442)
Discussing Prognosis (p. 453)

PROGNOSTIC TOOLS

PALLIATIVE PROGNOSTIC SCORE (PaP)

- **CLINICIAN PREDICTION OF SURVIVAL**—>12 weeks = 0, 11–12 weeks = 2, 7–10 weeks = 2.5, 5–6 weeks = 4.5, 3–4 weeks = 6, 1–2 weeks = 8.5
- **KARNOFSKY PERFORMANCE STATUS**—≥50% = 0, 10–40% = 2.5
- **ANOREXIA**—absent = 0, present = 1.5
- **DYSPNEA**—absent = 0, present = 1
- **TOTAL WBC**—4.8–8.5 = 0, 8.5–11 = 0.5, >11 = 1.5
- **LYMPHOCYTE PERCENTAGE**—20–40% = 0, 12–19.9% = 1, 0–11.9% = 2.5
- **UTILITY**—30 day survival for total score 0–5.5 = 97%, 5.6–11 = 59%, 11.1–17.5 = 25%

PALLIATIVE PROGNOSTIC INDEX (PPI)

- **PALLIATIVE PERFORMANCE SCALE**— ≥ 60% = 0, 30–50% = 2.5, 10–20 = 4
- **ORAL INTAKE**—normal = 0, moderately reduced = 1, severely reduced = 2.5
- **EDEMA**—absent = 0, present = 1
- **DYSPNEA AT REST**—absent = 0, present = 3.5
- **DELIRIUM**—absent = 0, present = 4
- **UTILITY**—with total score of 4 as cutoff, PPV for 6 week survival is 83%, NPV is 71%

PROGNOSTIC TOOLS (CONT'D)

PALLIATIVE PERFORMANCE SCALE (PPS)

PPS (%)	Mobility	Activity and evidence of disease	Self-care	Intake	LOC
100	Full	Normal activity and work No evidence of disease	Full	Normal	Full
90	Full	Normal activity and work Some evidence of disease	Full	Normal	Full
80	Full	Normal activity with effort Some evidence of disease	Full	Normal or reduced	Full
70	Reduced	Unable to do normal job Significant disease	Full	Normal or reduced	Full
60	Reduced	Unable to do hobby/house work Significant disease	Occasional assist	Normal or reduced	Full or confusion
50	Mainly sit or lie	Unable to do any work Extensive disease	Considerable assist	Normal or reduced	Full or confusion
40	Mainly in bed	Unable to do most activity Extensive disease	Mainly assist	Normal or reduced	Full or drowsy ± confusion
30	Totally bed bound	Unable to do any activity Extensive disease	Total care	Minimal to sips	Full or drowsy ± confusion
20	Totally bed bound	Unable to do any activity Extensive disease	Total care	Mouth care only	Full or drowsy ± confusion
10	Totally bed bound	Unable to do any activity Extensive disease	Total care		Drowsy or coma ± confusion
0	Dead	–	–	–	–

Management of Other Distressing Symptoms

SYMPTOM CONTROL MEASURES

PRINCIPLES OF SYMPTOM MANAGEMENT—the most critical aspect is to conduct a proper history and physical, along with targeted investigations, to identify and properly treat the underlying cause. The addition of palliative measures below may also improve quality of life

BLEEDING

- **NON-PHARMACOLOGIC MEASURES**—palliative radiation, arterial embolization and palliative surgeries may slow bleeding. Have dark towels by bedside in case of catastrophic bleed. Apply direct pressure and suction
- **PHARMACOLOGIC MEASURES**—antifibrinolytic agents (*tranexamic acid* 1000–1500 mg PO BID-TID, or 10 mg/kg IV q6–8 h, or 1–6.5 mg/kg/h IV after 10 mg/kg of loading dose, *aminocaproic acid* 4–5 g IV over first hour, then 1 g/h in 50 mL over 8 h). If catastrophic life-threatening bleed, consider giving *midazolam* 5 mg IV in syringe for rapid sedation

SYMPTOM CONTROL MEASURES (CONT'D)

COUGH

- **NON-PHARMACOLOGIC MEASURES**—consider endobronchial therapy for cancer airway lesions, high intrathoracic vagotomy in refractory severe cases
- **PHARMACOLOGIC MEASURES**—*benzonatate* 100 mg PO q8h PRN, *codeine* 7.5–60 mg PO

SYMPTOM CONTROL MEASURES (CONT'D)

BID, *dihydrocodeine* 5–10 mg PO TID, *hydrocodone* 5 mg PO BID, *morphine* 7.5–15 mg PO BID, *dextromethorphan* 10–30 mg PO q6h, *sodium cromoglycate* 10 mg NEB QID, *levodropropizine* 75 mg PO TID, *guaifenesin* 200–400 mg PO q4h or 600 mg PO BID, *gabapentin* 100–300 mg PO TID

DIARRHEA

- **NON-PHARMACOLOGIC MEASURES**—avoidance of laxatives, ensure adequate hydration
- **PHARMACOLOGIC MEASURES**—*loperamide* 4 mg PO qAM, then 2 mg PO after each loose stool (exclude *C. difficile* prior to treatment with antimotility agents), *diphenoxylate/atropine* 5 mg PO QID, *tincture of opium* 0.6 mL (6 mg, 10 mg/mL) PO q6h PRN. *Octreotide* 100–500 mcg SC TID may be considered for secretory diarrhea

HICCUPS—chlorpromazine, metoclopramide, haloperidol, methylphendiate

- **NON-PHARMACOLOGIC MEASURES**—breath holding, Valsalva maneuver, pressing on the eyeballs
- **PHARMACOLOGIC MEASURES**—*metoclopramide* 10 mg PO/IV q4h, *chlorpromazine* 25–50 mg PO QID, *haloperidol* 1–4 mg PO q4h, *baclofen* 5–20 mg PO TID

PRURITIS

- **NON-PHARMACOLOGIC MEASURES**—avoidance of irritants (e.g., soap), moisturizers, cooling lotions (e.g., calamine, Men-Phor), and barriers (e.g., occlusive dressings)

SYMPTOM CONTROL MEASURES (CONT'D)

- **PHARMACOLOGIC MEASURES**—antihistamines (e.g., *diphenhydramine* 25–50 mg PO q6–8 h, *loratadine* 10 mg PO daily), *naltrexone* 25–50 mg PO daily, *mirtazapine* 15–45 mg PO daily, *gabapentin* 100–300 mg PO TID, *aprepitant* 80 mg PO daily. For cholestasis induced pruritus, consider *cholestyramine* 4 g PO BID as first line, *rifampin* 300–600 mg PO daily as second line, and naltrexone as third line

SLEEP DISTURBANCE—trazodone, melatonin, mirtazapine, avoid benzodiazepines

THICK SECRETIONS—*guaifenesin* 200–400 mg PO q4h or 600 mg PO BID, *glycopyrrolate* 2–4 mg PO q4h

TASTE DISTURBANCE—*zinc sulfate* 200 mg PO BID ×14 days or 200 mg PO daily ×30 days

XEROSTOMIA—artificial saliva (*caphasol* 30 mL swish and swallow q4h)

EDEMA

- **LYMPHEDEMA**—consider non-pharmacological measures such as elevation, compression stockings, manual lymphatic drainage, complete decongestive therapy, and exercises. Diuretic therapy is often of limited effect
- **ANASARCA**—for selected patients with severe anasarca, consider *albumin* 25 g IV TID, *furosemide* 60 mg IV BID, fluid restriction

OVERREACTIVE BLADDER—*oxybutynin* 5 mg PO BID-QID

15
NUTRITION

Raj Padwal and Kari McKnight

Obesity

NEJM 2007 356:21; NEJM 2008 358:18

COMPLICATIONS AND ASSOCIATED DISORDERS

ENDOCRINE

- **INSULIN RESISTANCE**—hyperinsulinemia, prediabetes, type 2 diabetes
- **REPRODUCTION**—irregular menses, anovulatory cycles, infertility

CARDIOVASCULAR—hypertension, dyslipidemia (↑ chol, ↑ LDL or normal with small, dense particles, ↑ VLDL, ↑ TGL, ↓ HDL), coronary artery disease, heart failure, atrial fibrillation, stroke

RESPIRATORY

- **SLEEP APNEA**
- **OBESITY-ASSOCIATED HYPOVENTILATION SYNDROME** (Pickwickian syndrome; $PaCO_2$ ≥45 mmHg in absence of another cause)—↓ functional residual capacity, ↓ lung compliance, ↑ chest wall impedance, V/Q abnormalities (↓ ventilation but ↑ perfusion of lower lobes), ↓ strength and endurance of respiratory muscles, ↓ ventilatory drive, closure of small airways
- **PULMONARY HYPERTENSION**

GI—cholelithiasis, steatohepatitis, cirrhosis

GU—incontinence, kidney stones, glomerulopathy

MSK—osteoarthritis

NEUROLOGIC—pseudotumor cerebri

DERMATOLOGIC—striae, acanthosis nigricans, hirsutism, pressure sores

CANCER

- **BREAST**
- **GENITOURINARY**—prostate
- **GYNECOLOGICAL**—endometrial, ovarian
- **GASTROINTESTINAL**—esophagus, colorectal, liver, gallbladder, pancreas, stomach
- **KIDNEY**
- **NON-HODGKIN'S LYMPHOMA**
- **MULTIPLE MYELOMA**

PSYCHOSOCIAL—↓ education, ↓ employment, depression

PATHOPHYSIOLOGY

BODY MASS INDEX (BMI, weight/height^2)—under-weight <18.5 kg/m^2, normal 18.5–24.9 kg/m^2, overweight 25–29.9 kg/m^2, obesity ≥30–39.9 kg/m^2, severe or morbid obesity ≥40 kg/m^2

WAIST CIRCUMFERENCE

Ethnic group	Men	Women
Europid	≥94 cm [≥37 in.]	≥80 cm [≥31.5 in.]
South Asian, Chinese, Japanese	≥90 cm [≥35.4 in.]	≥80 cm [≥31.5 in.]

Waist circumference is a better predictor of cardiometabolic complications than BMI. Reproducibility is a concern. Use Europid cutoff points for South and Central American, sub-Saharan African, Eastern Mediterranean, and Middle Eastern populations until more specific data are available

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, Cr, AST, ALT, fasting glucose and/or HbA1C, lipid profile, TSH

SPECIAL

- **CARDIAC WORKUP**—after history and physical, consider ECG. Stress test if indicated
- **SLEEP APNEA WORKUP**—sleep study if clinical suspicion for obstructive sleep apnea
- **OBESITY HYPOVENTILATION WORKUP**—HCO_3 >27 mEq/L is a reasonable screening test. ABG to confirm hypercarbia. PFT and sleep study

MANAGEMENT

LIFESTYLE CHANGES—reduced calorie diet (estimated energy requirement with 500 kcal/day deficit would lead to weight loss of 0.5 kg/week for

D. Hui et al. (eds.), *Approach to Internal Medicine: A Resource Book for Clinical Practice*,
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MANAGEMENT (CONT'D)

first 3 months. A reduction of 5–10% of initial body weight is the minimal initial goal, as this correlates with improvement in comorbidities (≥10% usually required for clinically important improvements). Failing that, weight maintenance (no change from baseline weight) is the goal. Consult **dietitian** for dietary/behavior modification. **Exercise** (at least 150 min of moderate intensity physical activity/week). Consult **psychologist** if psychological issues (depression, abuse, binge eating, emotional eating) are major barriers to weight loss success

DRUG THERAPY—consider for patients with BMI >30 kg/m^2 or BMI >27 kg/m^2 if comorbid conditions. Aim to reduce >5% of initial body weight in 3–6 months. **Pancreatic lipase inhibitor** reduces fat absorption (*orlistat* 120 mg PO TID ac meals). **Satiety enhancement/multiple mechanisms** (*phentermine/extended-release topiramate* 15–92 mg PO qAM [risk of teratogenicity]; *lorcaserin* [5HT-2c agonist] 10 mg PO BID; *buproprion/naltrexone* 8/90–32/360 mg PO qAM). If drug therapy successful, indefinite use should be considered

SURGERY—consider for patients with BMI ≥40 kg/m^2 or BMI ≥35 kg/m^2 if comorbid conditions. Patients require lifelong post-operative follow-up. Surgery is the only treatment demonstrated to reduce mortality (**NEJM 2008 375:8**). **Gastric restriction procedures** (gastric banding [adjustable band squeezes and restricts upper gastric area] is safest but requires close follow-up and long-term outcomes inferior to other procedures; sleeve gastrectomy [resection of greater curvature gaining popularity]). **Malabsorptive/diversionary procedures** decrease absorption via bypass of parts of small intestine and also result in a variable amount of restriction of gastric size (Roux-en-Y gastric bypass, biliopancreatic diversion)

RISK REDUCTION—lipid control (see HYPERLIPIDEMIA p. 70). **Blood pressure control** (see HYPERTENSION p. 65). **Glycemic control** (see DIABETES p. 381)

TREATMENT ISSUES

OVERALL APPROACH

1. Identify overweight or obese adults using BMI and waits circumference
2. If BMI >25 kg/m^2, conduct clinical and laboratory investigations (heart rate, blood pressure, fasting glucose, lipid profiles), screen for depression, eating and mood disorders, and treat comorbidities and other health risks if present
3. Assess readiness to change behaviors
4. Devise goals and lifestyle modification program for weight loss and reduction of risk factors (5–10% of body weight or 0.5–1 kg/week [1.1–2.2 lb/week] for 6 months)
   - **NUTRITION**—reduce energy intake by 500–1000 kcal/day
   - **PHYSICAL ACTIVITY**—initially 30 min of moderate intensity 3–5×/week. Eventually ≥60 min on most days
   - **COGNITIVE BEHAVIORAL THERAPY**
5. Reassess progress
   - **SATISFACTORY**—regular monitoring. Reinforce lifestyle changes above. Address other risk factors. Periodic monitoring of weight, BMI, and waist circumference every 1–2 years
   - **NON-SATISFACTORY**—in addition to reinforcement of lifestyle changes, consider the following:
   - **PHARMACOTHERAPY**—if BMI ≥27 kg/m^2 plus risk factors or BMI ≥30 kg/m^2. Consider if patient has not lost 0.5 kg/week [1.1 lb/week] by 3–6 months of lifestyle changes
   - **BARIATRIC SURGERY**—if BMI ≥35 kg/m^2 plus risk factors or BMI ≥40 kg/m^2. Consider if other weight loss attempts have failed. Requires lifelong monitoring

Canadian Clinical Practice Guidelines 2006 CMAJ 2006 176:8

PREDICTIVE FACTORS FOR LONG-TERM WEIGHT CONTROL FROM THE NATIONAL WEIGHT CONTROL REGISTRY IN THE USA—low fat diet, regular self-monitoring of food intake and weight, physical activity (35 min of jogging per day or 80 min of brisk walking per day). Long-term follow-up and close patient–physician relationship important

RELATED TOPICS
Cardiovascular Disorders (p. 27)
Diabetes Mellitus (p. 381)
Hyperlipidemia (p. 70)
Hypertension (p. 65)
Fatty Liver (p. 143)
Sleep Apnea (p. 20)

Malabsorption Syndromes

See MALABSORPTION SYNDROMES (p. 140)

Anorexia–Cachexia

See ANOREXIA–CACHEXIA (p. 449)

Vitamin B12 Deficiency

DIFFERENTIAL DIAGNOSIS

DIET—strict vegans, older adults, alcoholics
GASTRIC—pernicious anemia, gastrectomy, gastritis, achlorhydria
PANCREATIC—insufficiency
SMALL BOWEL—malabsorption syndromes, ileal resection, Crohn's, blind loops, bacterial overgrowth
DRUGS—neomycin, metformin, proton pump inhibitors, N_2O

PATHOPHYSIOLOGY

DEFINITION OF VITAMIN B12 DEFICIENCY—vitamin B12 <148 pmol/L [<200 pg/mL]. Borderline is 148–222 pmol/L [200–300 pg/mL]. Normal values vary in different regions – check local laboratory ranges. Note that vitamin B12 is also called cobalamin (cbl)

VITAMIN B12 LEVELS—daily requirement 6–9 µg. Body store 2–5 mg. It takes years to deplete stores

VITAMIN B12 ABSORPTION PATHWAY

- **DIET**—vitamin B12–protein complex
- **IN STOMACH**—vitamin B12 in food is bound to protein. This is catalyzed by acid/pepsin (in stomach). Once released, vitamin B12 quickly binds to R factors produced in the saliva and gastric juice. This complex is not absorbable
- **IN DUODENUM**—pancreatic proteases break down B12–R factor bond. Vitamin B12 then binds to intrinsic factor (from stomach)
- **IN ILEUM**—absorption of vitamin B12–intrinsic factor complex

RELATED TOPICS
Macrocytic Anemia (p. 162)
Malabsorption (p. 140)
Vitamin Deficiencies (p. 141)

CLINICAL FEATURES

HISTORY—anemia, dyspnea, chest pain, fatigue, weight loss, dementia, paresthesia, weakness, falls, diet history, past medical history (gastritis, IBD, pancreatic disorders, bowel resection, alcoholism), medications

PHYSICAL—weight loss, lemon-colored skin tone (anemia and jaundice), dementia, decreased visual acuity, optic atrophy, Lhermitte's sign, anemia, atrophic glossitis, spasticity, weakness, hyperreflexia, clonus, decreased vibration, and proprioception but preserved pain and temperature sensation, abnormal heel–shin test, Romberg (unsteady with eyes closed), pronator drift, gait (altered proprioception, spastic), peripheral neuropathy, vaginal atrophy

SUBACUTE COMBINED DEGENERATION—lateral (corticospinal tract) and dorsal (vibration and proprioception) columns affected. Spinothalamic tract (pain and temperature) spared. Legs affected more than arms

INVESTIGATIONS

BASIC

- **LABS**—CBCD (megaloblastic anemia), peripheral smear (hypersegmented neutrophils), pancytopenia, bilirubin (↑), LDH (↑), vitamin B12, RBC folate

SPECIAL

- **SERUM ANTI-INTRINSIC FACTOR ANTIBODY**—sens 50–70%; spc near 100%
- **SERUM HOMOCYSTEINE LEVEL**—↑ if vitamin B12 deficiency. Perform if vitamin B12 level borderline
- **SERUM METHYLMALONATE LEVEL**—↑ if vitamin B12 deficiency. Perform if vitamin B12 level borderline
- **SCHILLING'S TEST**—rarely performed nowadays but may help to sort out etiology

INVESTIGATIONS (CONT'D)

- **FIRST STAGE**—administer radiolabeled cyano-Cbl 1–2 μg PO, then Cbl 1000 μg IM 1 h later to saturate tissue-binding sites and flush out any orally absorbed radiolabeled Cbl into the urine. A 24-h urine is collected. Normally 10–35% of radiolabeled oral dose is eliminated in the urine. If Cbl malabsorption, <8% is eliminated. Diagnostic possibilities include pernicious anemia, chronic pancreatitis, and ileal disease
- **SECOND STAGE**—if first stage is abnormal, repeat above but add oral intrinsic factor (after 4 weeks of vitamin B12 replacement). This helps to determine if vitamin B12 deficiency is related to pernicious anemia (improved absorption) vs. intestinal malabsorption (very low absorption)
- **OTHER VARIATIONS**—a trial of antibiotics (often 5 days of tetracycline) is given and the test is repeated again to investigate bacterial overgrowth syndrome. Another variation is to cook Cbl together with scrambled eggs. Patients with achlorydria will be unable to split Cbl from food proteins and urinary excretion of Cbl will be <10%

MANAGEMENT

TREAT UNDERLYING CAUSE—see above for list.
Vitamin B12 1000 μg SC/IM daily × 7 days, then 1000 μg SC/IM weekly for 1 month, and same dose monthly if pernicious anemia. Can continue with parenteral therapy or switch to oral (1–2 mg/day) once vitamin B12 levels are normalized. Alternatively, treatment with high dose oral cobalamin (1000–2000 mcg/day) can be used but parenteral replacement should be first line therapy in patients with neurologic deficit. Because absorption is variable, repeat levels to ensure they remain normal. Hematologic parameters improve within days to weeks; neurological often fail to remit fully on treatment, but improvement may be seen within months. Watch for hypokalemia, salt retention, and thrombocytosis early in the course of therapy

Diet and Supplemental Nutrition

INTRODUCTION

This chapter provides an overview of nutritional assessment, hospital diet types, enteral feeds, and supplemental parenteral nutrition
GENERAL ADVICE—for patients with significant under-nourishment or at risk of developing malnourishment (e.g. ICU patients, head and neck or esophageal cancer patients), consult dietitians for nutritional assessment and guidance regarding supplemental nutrition

NUTRITIONAL ASSESSMENT

FACTORS INFLUENCING ENERGY REQUIREMENTS—age, previous nutritional status, comorbidities (sepsis, obesity), activity
IDEAL BODY WEIGHT (IBW) CALCULATIONS (used to assess risk of malnutrition by comparing IBW with actual body weight)—the Hamwi Method is often used to provide initial estimate. IBW estimates from this method generally translates to a BMI of ≥19.7 for females and ≥20.8 for males

- ♂ **IBW** (kg) = (height in cm – 152 cm) × 1.1 + 48.2 kg OR in lbs = (height in inches – 60 in.) × 6 + 106 lbs

NUTRITIONAL ASSESSMENT (CONT'D)

- ♀ **IBW** (kg) = (height in cm – 152 cm) × 0.9 + 45.5 kg OR in lbs = (height in inches – 60 in.) × 5 + 100 lbs
- For small frame individuals, subtract 10%. For large frame, add 10%
- % IBW = (actual weight ÷ IBW) × 100
- Interpretation of % IBW **(JPEN 1977;1:11)**
  - Well-nourished >90% IBW
  - Mild malnutrition 80–90% IBW
  - Moderate malnutrition 70–79% IBW
  - Severe malnutrition <69% IBW
- If amputation is present, IBW estimation must be adjusted to account for the missing body part(s)
- BMI, % weight loss and % usual body weight (which compares current weight to usual weight) are also commonly used nutritional risk markers

DAILY ENERGY REQUIREMENTS

- **14 kcal/kg [6.4 kcal/lb] BODY WEIGHT**—BMI >40 kg/m^2
- **21 kcal/kg [9.5 kcal/lb] BODY WEIGHT**—BMI 30–39 kg/m^2

NUTRITIONAL ASSESSMENT (CONT'D)

- **25 kcal/kg [11.4 kcal/lb] BODY WEIGHT**—single organ failure, heavily sedated
- **30–40 kcal/kg [13.6–18.2 kcal/lb] BODY WEIGHT**—multi-organ failure, sepsis, trauma, postop major surgery

ESTIMATION OF BASAL METABOLIC RATE (BMR)

- **20 kcal/kg [9.1 kcal/lb] BODY WEIGHT**—can be used as a rough estimate
- **MIFFLIN-ST. JEOR EQUATION (Am J Clin Nutr 1990 51:2)**—validated for ambulatory adults and overweight or obese individuals:
- Male: RMR = [9.99 × wt (kg)] + [6.25 × ht (cm)]–[4.92 × age (years)] + 5
- Female: RMR = [9.99 × wt (kg)] + [6.25 × ht (cm)]–[4.92 × age (years)]–161
- **HARRIS-BENEDICT EQUATION—**tends to underestimate BMR in overweight and obese patients:
- Male: RMR = 66.47 + [13.75 × wt(kg)] + [5 × ht (cm)] – [6.76 × age(years)]
- Female: RMR = 655.1 + [9.56 × wt(kg)] + [1.85 × ht(cm)] – [4.68 × age (years)]
- Activity/Stress factors—the BMR or resting metabolic rate can be multiplied by a factor that captures stress or activity to calculate the total number of calories required

DAILY PROTEIN REQUIREMENTS

- **0.5–0.8** g/kg **[0.23–0.36** g/lb**] BODY WEIGHT** (protein restriction) for initial 48 h then **1.2–1.5** g/kg **[0.55–0.68 G/LB] BODY WEIGHT**—hepatic encephalopathy (note most cirrhotic patients suffer from malnourishment and protein restriction may not be warranted)
- **0.8–1** g/kg **[0.36–0.45** g/lb**] BODY WEIGHT** (protein restriction)—renal failure (no dialysis)
- **1–1.2** g/kg **[0.45–0.55** g/lb**] BODY WEIGHT**—not septic, minor trauma/surgery, non-malnourished, single system failure
- **1.2–1.5** g/kg **[0.55–0.68** g/lb**] BODY WEIGHT**—multi-organ failure, hemodialysis, sepsis, major trauma/surgery, closed head injury, malnutrition, peritoneal dialysis
- **1.5–2.0** g/kg **[0.68–0.91** g/lb**] (IDEAL) BODY WEIGHT**—multiple surgeries, trauma, severe burns, long bone fractures, peritonitis

FLUID REQUIREMENTS

- Fluid requirements are highly variable, depending on the patient's state of hydration, stress, and losses (e.g. ostomy losses). Fluid restrictions may be indicated in cases of heart failure, renal or liver failure, SIADH. Calculating fluid requirements can be done in two ways:
  - Age based approach:
    - 18–55 years = 35 mL/kg/day
    - 55–65 years = 30 mL/kg/day
    - 65 years = 25–30 mL/kg/day (minimum 1500 mL/day)
  - Weight based approach:
    - For the first 10 kg of body weight, give 100 mL/kg/day
    - For the second 10 kg of body weight, add 50 mL/kg/day
    - For each additional kg of body weight, add 20 mL/kg/day if ≤50 years of age OR 15 mL/kg/day if >50 years of age

HOSPITAL DIET TYPES

STANDARD—regular, full fluid, clear fluid

THERAPEUTIC—heart healthy, diabetic, renal (predialysis, hemodialysis, peritoneal dialysis), sodium restricted (2 g Na, 4 g Na), fiber restricted, high protein/cal

SPECIAL—diets for cultural/religious modifications, disease-specific requirements (e.g. gluten free), various nutrient-specific therapeutic modifications (e.g. high K^+, purine restricted), neutropenic, post-gastrectomy

DIET CONSISTENCY MODIFICATIONS

- **MODIFIED SOLIDS**—pureed, diced, diced dysphagia, easy to chew, minced
- **THICKENED FLUIDS**—level 1 (nectar), level 2 (honey), level 3 (pudding)
- **NOTE:** if dysphagia suspected, consider swallowing assessment to determine most appropriate consistency

ENTERAL NUTRITION OVERVIEW

ADVANTAGES—maintains gut integrity and immunologically favorable compared to total parenteral nutrition

CONTRAINDICATIONS—hemodynamically unstable, severe ileus, bowel obstruction, UGI bleed, distal anastomosis, NG output >1 L/24 h, high output proximal fistula, uncontrollable nausea, vomiting and/or diarrhea, short gut, radiation enteritis

ROUTES FOR ENTERAL FEEDS

- **NASOGASTRIC/KAOFEED/OROGASTRIC TUBE**—expected use <6 weeks. Risk of aspiration (orogastric used for patients with basal skull fractures or choanal atresia)

ENTERAL NUTRITION OVERVIEW (CONT'D)

- **NASOJEJUNAL TUBE**—expected use <6 weeks. Less chance of aspiration/pneumonia; used for patients with high risk aspiration, delayed gastric emptying, or who require feeding past ligament of Treitz (e.g. pancreatitis)
- **GASTROSTOMY TUBE**—expected use >6 weeks. Risk of aspiration
- **JEJUNOSTOMY TUBE**—expected use >6 weeks. Decreased aspiration risk (used for long term post-pyloric feeds)

ADMINISTRATION OF ENTERAL FEEDS

- **CONTINUOUS**—usually given over 24 h. Compared to bolus feed, decreased aspiration risk, and better glycemic control. Start full strength formula at 25 mL/h, increase by 25 mL q4h to goal rate. Check gastric residuals q4h and continue to increase if <250 mL. If >250 mL, hold feeds, initiate pro-motility therapies, and re-check after 4 h
- **NOCTURNAL**—for patients eating 50% of requirements during daytime; wean off tube feed
- **BOLUS/INTERMITTENT**—for more mobile patients. More physiologic. Start with 1 can (250 mL) over 30–60 min 4×/day

ENTERAL NUTRITION FORMULAS

- **ISOSOURCE HN**—1.2 kcal/mL, goal usually 60–85 mL/h; 0.053 g protein/mL. Fiber containing. Standard formula
- **ISOSOURCE 1.5**—1.5 kcal/mL, 0.068 g protein/mL, fiber containing
- **RESOURCE 2.0**—2.025 kcal/mL, 0.084 g protein/mL. For fluid-restricted patients
- **PERATIVE**—1.3 kcal/mL, 0.067 g protein/mL arginine containing, lower in fat
- **NOVASOURCE RENAL**—2 kcal/mL, 0.074 g protein/mL For renal patients on dialysis or prerenal with high electrolytes
- **ISOSOURCE VHN**—1 kcal/mL, 0.063 g protein/mL. For catabolic patients, high protein
- **RESOURCE DIABETIC**—1.06 kcal/mL, 0.064 g protein/mL. Higher fat, low carbs, fiber containing. For difficult to control blood sugars.
- **PEPTAMEN 1.5**—1.5 kcal/mL, 0.068 g protein/mL. Semi-elemental (low residue). Used for patients with malabsorption problems, severe diarrhea
- **PEPTAMEN AF 1.2 with PREBIO**—1.2 kcal/mL, 0.0756 g protein/mL. Semi-elemental (low residue), higher protein, contains EPA/DHA and fructo-oligosaccharides (FOS)/inulin (soluble fiber). For highly stressed individuals who may experience inflammation or feeding intolerance (malabsorption)
- **PULMOCARE**—1.5 kcal/mL, 0.063 g protein/mL. Low carbohydrate to lower CO_2 production. For patients with COPD or CO_2 retention

ADDITIONS TO ENTERAL FEEDS

- **PECTIN**—20 mL BID. Soluble fiber to decrease diarrhea
- **BENEPROTEIN**—one scoop = 6 g protein and 25 kcal
- **GLUTAMINE**—main fuel for gut enterocytes. For burns and trauma. Consult dietitian for recommendations

COMPLICATIONS OF ENTERAL FEEDS

- **DIARRHEA**—due to osmotic load/rapid feeding rate, contamination, medications, gastroenteritis, *Clostridium difficile*
- **VOMITING**—associated with aspiration
- **ASPIRATION**—prevent by using small bore feeding tube (<10 Fr), monitor tube migration, post-pyloric position of tube, continuous schedule, elevation of head of bed by >30° during feeding, positioning of patient on right side, ambulation, use of promotility agents 30 min before feeding (*metoclopramide* 10 mg PO QID) to decrease post-feed gastric residual volumes, ensure bowel routine

TUBE OBSTRUCTION

- **CONSTIPATION**—due to reduced bowel motility, dehydration/inadequate free water, inadequate fiber, bowel obstruction

PARENTERAL NUTRITION OVERVIEW

TOTAL PARENTERAL NUTRITION (TPN)

- **INDICATIONS**—unusable GI tract for at least 5–7 days. Bowel resection/obstruction/fistula without distal feeding access, intractable diarrhea/malabsorption/vomiting, acute GI bleed, failure of enteral nutrition to meet nutritional feeds, short gut, prolonged ileus, mesenteric ischemia, radiation enteritis
- **CONTRAINDICATIONS**—GI tract usable and capable of absorbing adequate nutrients to meet requirements within 3–5 days/dependence on TPN <5 days, well-nourished patient with minimal stress or trauma where GI tract usable in <7 days, non-survivable injury/illness, aggressive support not desired, risks of TPN outweigh benefits, inability to obtain appropriate venous access, severe hemodynamic instability

PARENTERAL NUTRITION OVERVIEW (CONT'D)

- **COMPLICATIONS**—no GI tract mucosal growth, no maintenance of gut barrier, metabolic disturbances if overfeeding (hyperglycemia, cholestasis/hepatic steatosis, electrolyte imbalances, refeeding syndrome), volume overload, line sepsis

PERIPHERAL PARENTERAL NUTRITION (PPN)—short-term use only as nutritionally inadequate; addition of low-dose heparin and hydrocortisone to prevent line thrombosis; must be <1000 mOsm, usually requires larger volumes of fluid for kcal/protein delivery

COMPONENTS OF TOTAL PARENTERAL NUTRITION

- **TRAVASOL**
- **PROTEIN**—4 kcal/g, 10% amino acid
- **CARBOHYDRATE**—3.4 kcal/g; 70% dextrose solution
- **LIPID**—2 kcal/mL; 20% lipid emulsion. Note: for patients receiving propofol, (dispensed in a 10% lipid emulsion; 0.1 g fat/mL), this source of energy (1.1 kcal/mL) must be taken into account in the overall nutrition prescription
- **ELECTROLYTES**—Na (1–2 mmol/kg/day), K (60–120 mmol/day or 1–2 mmol/kg/day), Ca (10–15 mmol/day), Mg (8–20 mmol/day), PO_4 (20–40 mmol/day)
- **MICRONUTRIENTS**—multivitamin solution (10 mL/day), vitamin K (5–10 mg/week) as required, trace element solution (1 mL/day), acetate as required; insulin and H_2 antagonists as indicated

DAILY LIPID REQUIREMENTS (FOR PARENTERAL NUTRITION)

- **0.8–1 g/kg [0.36–0.45 g/lb] (IDEAL) BODY WEIGHT.** No more than 30% of energy as fat and no more than 10% saturated fat. At least 2–4% of total caloric intake should be essential fatty acids to prevent deficiency states

DAILY CARBOHYDRATE REQUIREMENTS (FOR PARENTERAL NUTRITION)

- **2–4** mg/kg/min (start low and go slow if concern regarding refeeding syndrome)

REFEEDING SYNDROME

RISK FACTORS—severe malnutrition/chronic malnutrition due to underfeeding/chronic disease, anorexia nervosa, cancer, alcoholism, severe unintentional weight loss/morbid obesity with massive weight loss, prolonged fasting (7–10 + days)

MECHANISM—carbohydrate administration leading to a sudden shift from fat to carbohydrate metabolism → ↑ insulin secretion → stimulates cellular uptake of phosphate → ↓ Mg, ↓ PO_4, ↓ K. Key complications include cardiac (impaired contractility, heart failure, arrhythmias), neurological (seizures) and respiratory/muscular weakness

TIME FRAME—usually occurs within 3 days of initiation of feed (parenteral, enteral feed, oral intake, IV glucose)

MANAGEMENT—start carbohydrate/feeds low and increase slowly. Monitor electrolytes (lytes, Mg, PO_4 daily × 3 days and replete PRN), monitor glycemic control, monitor fluid balance/signs of edema/fluid overload and weight, vitamin supplementation (e.g. thiamine 100 mg IV/PO daily for 5–7 days, folic acid 1 mg/day)

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OBSTETRIC MEDICINE

Eliana Castillo and Tammy Shaw

Physiologic Changes in Pregnancy

CLINICAL IMPLICATIONS—to maintain adequate uterine perfusion, fetal oxygenation, and nutrient delivery. May potentially mask serious illness

IMPORTANT CHANGES IN PREGNANCY

	Change	Clinical Implication
Core temperature	Unchanged	Fever should be investigated and treated; maternal fever is teratogenic in T_1, and associated with adverse perinatal outcomes in T_3
Upper airway	↑ edema and friability (hyperemia and glandular function)	Nasal congestion, epistaxis and snoring common. Failed/difficult intubation more common than non-pregnant state
Thorax	↑ circumference, elevated diaphragm (~4 cm) but normal excursion	Anatomical landmarks for thoracentesis shifted. ECG changes: QRS axis deviates to left in late pregnancy ± T-wave inversion ± ST depression in inferior and lateral leads
Tidal volume	↑ early in T_1 at expense of FRC/RV	Expected PaO_2 100–110 mmHg, $PaCO_2$ 28–32 mmHg (mild respiratory alkalosis), HCO_3 18–21 mmol/L (compensatory reduction), arterial pH 7.40–7.45 (normal/slight alkalosis). An elevated RR should be investigated
Respiratory rate	Minimal increase by ~3–4 breaths/min at term	
Minute ventilation (RR × TV)	↑ by 50% at term	
Oxygen consumption	↑ by 15–20%	
Heart rate	↑ by 15–20 beats/min by T_3	Pregnancy may unmask heart disease, especially obstructive lesions. Exacerbation of pre-existing tachyarrhythmias or *de novo* presentations also possible. Compression of IVC by gravid uterus in supine position may ↓ cardiac output by up to 25% left lateral decubitus position recommended Greatest risk of cardiac decompensation between 28 and 32 weeks gestation (maximum increase in maternal blood volume), during labor (hemodynamic changes), and in post-partum period (fluid shifts)
Stroke volume	↑	
Cardiac output (HR × SV)	↑ by 30–50% (peaks ~28 weeks)	
Ejection fraction	Unchanged	

D. Hui et al. (eds.), *Approach to Internal Medicine: A Resource Book for Clinical Practice*,
DOI 10.1007/978-3-319-11821-5_16, © Springer International Publishing Switzerland 2016

IMPORTANT CHANGES IN PREGNANCY (CONT'D)

	Change	Clinical Implication
Systemic vascular resistance	↓	
Blood pressure	↓ by 10–15 mmHg (nadir at ~20–24 weeks) with gradual increase back to baseline	↓↓ DBP > ↓ SBP → widened pulse pressure
Renin-angiotensin-aldosterone system	Upregulated	↑↑ renin, ↑ aldosterone, ↓ aldosterone/renin ratio in response to systemic vasodilation and ↓ SVR
Renal blood flow	↑ by 80%	
Glomerular filtration rate	↑ by 40–50%	Hyperfiltration with ↓ in serum Cr to ~35–70 mmol/L [0.4–0.8 mg/dL]; higher levels suggest renal disease. Dose adjustments for renally-cleared drugs may be required
Plasma volume	↑ by 30–50% (1.1–1.6 L) by T_3	JVP height remains normal
RBC mass	↑ by 40%	Iron requirements ↑ by 50%. Disproportionate ↑ in plasma volume results in physiologic anemia (hemoglobin ↓ by ~20 g/L [2 g/dL] by T_3)
Coagulation system	↑ levels of coagulation factors, decreased fibrinolysis	10× ↑ risk for venous thromboembolism during pregnancy and up to 6 weeks postpartum
Gastric pH	↑	Impaired drug absorption, dose adjustments may be required
Lower esophageal sphincter pressure	↓ (progesterone effect)	GERD, nausea and vomiting common. ↑ risk of aspiration with intubation
GI motility	↓	Constipation and abdominal bloating common. Impaired drug absorption, dose adjustments may be required
Hepatic metabolism	Changes in drug metabolism (e.g., cytochrome P450 system enzymes may be ↑ or ↓)	Dose adjustments may be required for hepatically-metabolized medications (e.g., antiepileptics)
Biliary system	↓ motility, ↑ bile cholesterol secretion and saturation	↑ risk for gallstones during pregnancy
Thyroid	↑ thyroid gland size by 18%. ↑ estrogen → ↑ thyroxine-binding globulin → total T4 and ↑ total T3 (but free T4 and free T3 mostly remain normal)	Thyroid function tests should be interpreted using trimester-specific TSH and total T4 reference ranges for pregnant women. For those already on levothyroxine replacement, ~75% of women will require an increased dose during pregnancy. Homology between hCG and TSH can result in hCG mediated hyperthyroidism during pregnancy
Glucose metabolism	↑ insulin resistance (peak ~30 weeks gestation) from human placental lactogen and progesterone	Screen for gestational diabetes by 24–28 weeks gestation

MATERNAL MORTALITY AND RESUSCITATION

MATERNAL MORTALITY—defined as death during pregnancy or up to 1 year postpartum. Most common causes include cardiovascular disease, venous thromboembolism, amniotic fluid embolus, obstetric hemorrhage, infection (sepsis), suicide, and preeclampsia/eclampsia

MATERNAL RESUSCITATION—follow ACLS algorithm for non-pregnant adult population including medications, dosages (for medications, defibrillation, cardioversion, pacing), compressions, and ventilation rate. Special considerations include: (1) obtaining venous access above the diaphragm (potential obstruction from gravid uterus below diaphragm); (2) chest compressions performed higher up on sternum; (3) left uterine displacement (first-line) or left lateral tilt (second-line) to relieve aorto-caval compression by gravid uterus; (4) difficult airway and ventilation requires expertise; (5) perimortem caesarean section if no return of spontaneous circulation within 4 min; (6) remove fetal monitors for defibrillation if possible (theoretical risk to fetus). *Do not delay treatment: healthy baby requires healthy mother!*

Preeclampsia/Eclampsia/HELLP Syndrome

JOGC 2014 36:5
SOGC Hypertensive Disorders of Pregnancy 2014 Guidelines

DIFFERENTIAL DIAGNOSIS OF HYPERTENSION IN PREGNANCY

PREEXISTING (CHRONIC) HYPERTENSION—SBP ≥140 and/or DBP ≥90 mmHg prior to 20th week of gestation, complicates 1% of pregnancies: 20% risk of developing preeclampsia

PREECLAMPSIA SUPERIMPOSED UPON PREEXISTING HYPERTENSION—preexisting (chronic) hypertension with new or worsening proteinuria (≥300 mg/day with 24-h urine collection or ≥30 mg/mmol on spot urine protein/Cr ratio), or resistant hypertension (i.e., resistance to ≥3 antihypertensive drugs), or development of adverse condition (see list below), or development of severe complication (see list below) at ≥20 weeks gestation. *Diagnosis of preeclampsia does not require presence of proteinuria*

GESTATIONAL HYPERTENSION—new-onset hypertension ≥20 weeks gestation, complicates 5–6% of pregnancies. 35% risk of developing preeclampsia

PREECLAMPSIA SUPERIMPOSED UPON GESTATIONAL HYPERTENSION—new-onset proteinuria, or development of adverse condition (see list below), or development of severe complication (see list below) after onset of gestational hypertension

PREECLAMPSIA—occurring *de novo*, defined as gestational hypertension, with either proteinuria, adverse condition, or severe complication

PATHOPHYSIOLOGY

MECHANISMS—multifactorial involving immunologic, genetic and maternal factors that lead to uteroplacental mismatch and endothelial cell dysfunction

ADVERSE CONDITIONS OF PREECLAMPSIA—headaches/visual symptoms, chest pain/dyspnea, oxygen saturation <97%, nausea, vomiting, elevated liver enzymes or creatinine, thrombocytopenia, hyperuricemia, oligohydramnios, IUGR, abnormal uterine artery or umbilical cord Doppler flow. SBP ≥160 mmHg most important predictor of fatal stroke among women with hypertensive disorders in pregnancy

SEVERE COMPLICATIONS OF PREECLAMPSIA—generalized tonic-clonic seizures (eclampsia), PRES (posterior reversible leukoencephalopathy syndrome), cortical blindness/retinal detachment, altered level of consciousness, stroke, pulmonary edema, acute kidney injury, hepatic dysfunction/hematoma/rupture, hemolysis, placental abruption, fetal demise. HELLP (Hemolysis, **E**levated **L**iver **E**nzymes, **L**ow **P**latelets) syndrome = constellation of findings considered variant of severe preeclampsia

RISK FACTORS—extremes of age (<18, >40), nulliparity, multiple gestations, prior preeclampsia, obesity, chronic hypertension, diabetes mellitus, chronic kidney disease, antiphospholipid antibodies, and inter-pregnancy interval ≥10 years

PATHOPHYSIOLOGY (CONT'D)

CAUSES OF DEATH—hemorrhagic stroke from uncontrolled hypertension and eclampsia

CLINICAL FEATURES

HISTORY—inquire about headaches, visual disturbances, epigastric or RUQ pain, nausea, vomiting, swelling, decreased fetal movements

PHYSICAL—check vitals, look for retinal vasospasm, heart failure, edema (facial, limbs), RUQ tenderness, hyperreflexia and clonus

INVESTIGATIONS

BASIC

- **LABS**—CBCD, Cr, spot urine for protein to creatinine ratio, AST, ALT, albumin, uric acid (hyperuricemia associated with preeclampsia)

SPECIAL

- **BLOOD TESTS**—peripheral smear, lytes, urea, bilirubin, INR, LDH if indicated
- **FETAL EFFECTS**—biophysical profile and fetal US

MANAGEMENT

ACUTE—ABC, O_2 to keep sat >95%, IV with judicious fluid

ACUTE LOWERING OF SEVERE HYPERTENSION (SBP ≥160 mmHg or DBP ≥110 mmHg)—*labetalol* (start with 20 mg IV, repeat 20–80 mg IV q10–30 min, or infusion 1–2 mg/min, max 300 mg), *nifedipine short-acting capsule* 5–10 mg PO q30min, or *hydralazine* (start with 5 mg IV, repeat 5–10 mg IV q20–30 min, max 20 mg). Severe cases may require continuous infusion. Consider urgent delivery if not controlled

CHRONIC MANAGEMENT OF NON-SEVERE HYPERTENSION (SBP 140–159 mmHg or DBP 90–109 mmHg)—target BP at 130–140/80–90 mmHg if renal disease, diabetes, cardiovascular disease, or cerebrovascular disease. Otherwise target BP 130–155/80–105 mmHg; tighter control (DBP 85 mmHg [vs. 100 mmHg]) results in less severe hypertension without significant ↑ risk of adverse fetal outcomes. *Labetalol* 100–400 mg PO BID–TID, max 1200 mg/day, *nifedipine XL* 20–60 mg PO daily, max 120 mg/day, or *methyldopa* 250–500 mg PO BID–TID, max 3 g/day are good first-line choices. Avoid ACE inhibitors, ARBs, atenolol and prazosin. Second-line: other β-blockers and hydralazine. Third line: other CCBs, clonidine, and thiazide diuretics

MANAGEMENT (CONT'D)

SEIZURE PREVENTION AND TREATMENT—*MgSO4* 4 g IV bolus, then 1–2 g/h × 24–48 h. Re-bolus for ongoing seizures. Monitor for magnesium toxicity (respiratory depression, hypotension, muscle weakness, hyporeflexia) and give calcium gluconate if toxic. $MgSO_4$ is contraindicated in myasthenia gravis (may precipitate myasthenic crisis). Benzodiazepines, phenytoin and phenobarbital can be considered as adjunctive therapy if ongoing seizures despite $MgSO_4$

DELIVERY—the cure for preeclampsia, eclampsia, and HELLP. Administer steroids to promote fetal lung maturation prior to 34 weeks if early delivery

POSTPARTUM—gestational hypertension, preeclampsia/eclampsia/HELLP syndrome can present *de novo* or worsen in the postpartum period. Blood pressure can increase on days 3–6 postpartum. Monitor and continue antihypertensive therapy. Gestational hypertension/hypertension related to severe preeclampsia expected to resolve within 6–12 weeks. Metabolic abnormalities (e.g., proteinuria) that do not resolve by 3–6 months require further work-up

RECURRENCE—preeclampsia recurrence rate 10–40%. Consider antiphospholipid syndrome screen if preeclampsia or placental insufficiency <34 weeks. *ASA* 81 mg PO daily before 16 weeks gestation during next pregnancy and supplemental calcium 1000 mg/day (in women with dietary calcium intake <600 mg/day) recommended for prevention

LONG-TERM—history of hypertensive disorders in pregnancy increases risk for chronic hypertension, cardiovascular events, cerebrovascular accidents, renal disease, type 2 diabetes, and hypothyroidism. Lifestyle changes and routine vascular risk factor screening essential. Women with history of preeclampsia may experience post-traumatic stress disorder; monitor and provide mental health support

Related Topics
Hypertension (p. 65)
Proteinuria (p. 85)
Seizures (p. 350)

Pulmonary Diseases in Pregnancy

ASTHMA

TREATMENTS—similar to non-pregnant patients. β-agonists, anticholinergics, and glucocorticoids (inhaled, systemic) are safe. Leukotriene antagonists if refractory. Keep O_2 sat >95% to prevent fetal hypoxia. Consider stress dose steroids during delivery if patient required moderate systemic steroids for >3 weeks in the preceding year

VENOUS THROMBOEMBOLISM

PATHOPHYSIOLOGY—increased risk of DVT/PE due to ↑ factors I, VII, VIII, IX, X, von-Willebrand factor, and fibrin, ↓ protein S and fibrinolytic activity, and increased resistance to activated protein C, especially during T3. Also stasis due to ↓ venous tone and flow. Similar risk of DVT/PE in each trimester but highest postpartum; 90% of DVT in pregnancies are left sided and majority are pelvic

DIAGNOSIS—if suspect venous thromboembolism, consider initiation of LMWH while waiting for investigations. For DVT workup, perform compression US; if pelvic vein DVT suspected, consider MRV pelvis, Doppler study, or (postpartum) CT of pelvic veins. Otherwise, repeat compression US in 5–7 days if still symptomatic. For PE workup, perform V/Q scan if CXR normal (note: if Q normal, can skip V portion of scan). If CXR abnormal and/or V/Q scan nondiagnostic, proceed with CT chest. CT chest is associated with lower fetal radiation exposure than V/Q scan in T_1–T_2, but higher risk of maternal breast cancer (14% increased lifetime risk)

RADIATION RISKS—fetal exposure of <5 cGy [5 rad] accumulatively in each pregnancy is acceptable, but oncologic effects controversial (e.g., childhood leukemia). Consider proximity of fetus to radiations site (i.e., radiation from CT chest > V/Q scan in T_3) and limit where possible (i.e., abdominal shields)

FETAL RADIATION EXPOSURE FOR COMMON IMAGING MODALITIES

Imaging	Estimated fetal radiation exposure (rad)
Ultrasound	None
CXR	<0.001
CT head	<0.001
V/Q scan	0.01–0.02 ventilation (V) 0.01–0.03 perfusion (Q)

VENOUS THROMBOEMBOLISM (CONT'D)

Imaging	Estimated fetal radiation exposure (rad)
CT chest (PE protocol)	0.0003–0.002 (T_1) 0.0008–0.0077 (T_2) 0.005–0.013 (T_3)
Pulmonary angiogram	<0.05 via brachial route 0.2–0.3 via femoral route
Cardiac angiogram	<1
AXR	0.2–0.3
IVP	0.8 (complete series) 0.2 (limited series)
MRI/MRV/MRA	None

Related Topics
Asthma (p. 1)
Pulmonary Embolism (p. 10)

TREATMENT—LMWH dosed using current weight (not pre-pregnancy or ideal body weight). Consider monitoring of anti-Xa level (4–6 h after last dose, target 0.6–1.2 IU/mL). Duration of therapeutic anticoagulation 3–6 months, then transition to prophylactic dose of LMWH until end of 6 weeks postpartum. If neuraxial analgesia, hold therapeutic LMWH × 24 h and prophylactic LMWH × 12 h beforehand. If unable to hold anticoagulation (e.g., acute clot <4 weeks), consider bridging with IV unfractionated heparin (and hold when in active labor or 2 h prior to cesarean section), and/or consider IVC filter. Systemic thrombolysis generally contraindicated (risk of fetal demise). Warfarin not recommended during pregnancy (teratogenic in T_1; associated with fetal CNS hemorrhage/malformations, miscarriage, stillbirth, neonatal demise). May consider warfarin as an alternative to LMWH in the postpartum period while breastfeeding

FUTURE PREGNANCIES—provide antepartum and postpartum thromboprophylaxis to women with significantly increased risk (>1% absolute risk) of venous thromboembolism. Therapeutic-dose anticoagulation if already on long-term anticoagulation for established indication. Intermediate or therapeutic-dose if prior history of venous thromboembolism and high-risk thrombophilia (e.g., APLA, antithrombin defiency), but not previously on anticoagulation. Prophylactic dose if prior history of venous

VENOUS THROMBOEMBOLISM (CONT'D)

thromboembolism (unprovoked, related to oral contraceptive pill, related to pregnancy, or in setting of low-risk thrombophilia), or for asymptomatic thrombophilia (e.g., homozygote with factor V Leiden mutation, homozygote prothrombin gene mutation, antithrombin deficiency)

OTHER CONSIDERATIONS—compression stockings for symptom management. Caution against use of combined oral contraceptive pills. Consider thrombophilia work-up, if appropriate, according to clinical scenario and patient preference

NEJM 2008 359:19
JOGC 2014 36:6

AMNIOTIC FLUID EMBOLISM

PATHOPHYSIOLOGY—can occur during labor and delivery or with uterine manipulation. Risk factors include older age and multiparity. Amniotic fluid enters maternal circulation → inflammation, vasospasm, and venous occlusion → cardiogenic shock and respiratory failure

DIAGNOSIS—clinical diagnosis with classic triad of sudden-onset dyspnea and hypoxia, hypotension, and coagulopathy. Differential diagnosis includes septic shock, pulmonary embolism, aspiration pneumonia, uterine rupture, abruptio placentae, and venous air embolism

TREATMENTS—supportive, supplemental O_2, hemodynamic support (vasopressors ± IV fluids), ICU admission. Rapid delivery of the fetus (beware of risk of rapid blood loss with coagulopathy; may potentially require PRBC, FFP, platelet, and/or cryoprecipitate transfusion)

COMPLICATIONS—at least 20% maternal mortality, 25–50% of which die within the first hours of onset of the disease. Patients who survive are at high risk for ARDS, acute renal injury, and neurological complications due to cerebral hypoxia (up to 85%)

Cardiac Diseases in Pregnancy

PATHOPHYSIOLOGY

HIGH-RISK CARDIOPULMONARY CONDITIONS—generally advise against getting pregnant if any of the following conditions: tetralogy of Fallot with severe cyanosis, Eisenmenger's syndrome, severe pulmonary hypertension, functional limitation NYHA 3 or 4, recent cardiac transplantation with high-dose immunosuppression, Marfan's syndrome with aortic root >40 mm [1.6 in.], interstitial pulmonary fibrosis, lymphangioleiomyomatosis, and active lung cancer

Related Topics
Endocarditis (p. 60)
Heart Failure (p. 37)
Valvular Disorders (p. 59)

VALVULAR DISORDERS

REGURGITANT VALVULAR HEART DISEASE—may improve during pregnancy due to ↓ systemic vascular resistance

STENOTIC VALVULAR HEART DISEASE—may worsen during pregnancy. Symptomatic or severe stenosis should be evaluated for correction prior to pregnancy. Valvuloplasty during pregnancy may be considered for worsening symptoms. β-blockers to decrease HR in mitral stenosis.

VALVULAR DISORDERS (CONT'D)

Supportive measures with aggressive pain control and early neuraxial analgesia during labor. Assist second stage of labor with vacuum or forceps. Avoid fluid overload

PROSTHETIC HEART VALVE—for mechanical valves, continue oral anticoagulation until conception. During T_1 (within first 6 weeks), switch to therapeutic dose LMWH given BID (target anti-Xa level 0.7–1.2 IU/mL, 4–6 h after last dose), but avoid warfarin (teratogenic, ↑ risk if >5 mg/day). During T_2-T_3 and up until 36 weeks gestation, treatment options include therapeutic LMWH given BID *or* warfarin (target INR 2.5–3.5). Choice of anticoagulation depends on risk of thrombosis (i.e., type of valve) and patient preference. Consider either LMWH *plus* ASA 81 mg PO daily, or warfarin for highly thrombogenic valves (i.e., mitral position, older generation mechanical valve, history of thromboembolism). Warfarin more effective for prevention of valvular thrombosis but associated with higher risk of fetal CNS hemorrhage/malformations, miscarriage, stillbirth, neonatal demise. At 36th week, anticoagulation should be switched to unfractionated heparin in preparation for delivery, and allow at least 10–14 days for (fetal) warfarin washout. Preconception counseling highly recommended

VALVULAR DISORDERS (CONT'D)

ENDOCARDITIS PROPHYLAXIS—not recommended for vaginal delivery and cesarean sections. May consider for select high-risk cardiac conditions (i.e., prosthetic valve, unrepaired cyanotic congenital heart defect, repaired cyanotic congenital heart defect with residual defects, cardiac transplant recipients with valvulopathy, previous endocarditis)

MYOCARDIAL DISORDERS

PERIPARTUM CARDIOMYOPATHY—dilated cardiomyopathy with LVEF <45% during last month of pregnancy or within 5 months postpartum in the absence of previous heart disease. Diagnosis of exclusion. Medical management similar to treatment of HF in non-pregnant individuals with diuretics, β-blockers (except atenolol, risk of fetal growth retardation), nitrates, hydralazine, and digoxin. When pregnant, ACE inhibitors and ARBs are contraindicated, and aldosterone antagonists should be avoided if possible. When breastfeeding, ACE inhibitors (enalapril, captopril) and aldosterone antagonists (spironolactone) may be used. Anticoagulate if LVEF <35% or atrial fibrillation. Overall prognosis variable

MYOCARDIAL DISORDERS (CONT'D)

(mortality in up to 30%, around 25–50% have full recovery of myocardial function within 6 months, and 4–7% have progressive disease eventually requiring cardiac transplant). Recurrence in up to 30% with high risk of mortality in subsequent pregnancy if persistent ↓ LVEF. Preconception counseling highly recommended

ISCHEMIC HEART DISEASE—stress echocardiogram (preferred), exercise stress test, MIBI, and angiograms (beware radiation) can be considered for investigations

RHYTHM DISORDERS

PALPITATIONS—sinus tachycardia and ectopic beats are common. Increased SVT in patients previously diagnosed with SVT. May treat with adenosine, β-blockers (except atenolol), calcium channel blockers, or digoxin. DC cardioversion if unstable (remove fetal monitors if possible [theoretical risk to fetus] but do not delay treatment). Investigate for underlying arrhythmia, structural abnormality (cardiomyopathy, valvular disease), and precipitant (PE, sepsis, thyrotoxicosis) as appropriate

Cleve Clin J Med 2004 71:12

Hepatic Diseases in Pregnancy

DIFFERENTIAL DIAGNOSIS

PREGNANCY-RELATED LIVER DISEASE—hyperemesis gravidarum, preeclampsia/eclampsia/HELLP syndrome, intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy

- **HYPEREMESIS GRAVIDARUM** (T1–2, incidence 0.3–1%)—**nausea, vomiting**, weight loss, ↑ ALT >AST, N bili
- **PREECLAMPSIA/ECLAMPSIA** (T2–3, incidence 5–10%)—see section under preeclampsia
- **HELLP SYNDROME** (T3, incidence 0.1%)—preeclampsia symptoms. ↑ ALT, ↑ AST, ↑ bilirubin, ↓ platelets, ↑ LDH. May progress to DIC (30%)
- **INTRAHEPATIC CHOLESTASIS OF PREGNANCY** (T2–3, incidence 0.1–0.2%)—functional disorder of bile formation with severe **pruritus**. Jaundice in 20–60%, occurs 1–4 weeks after pruritus starts. ↑ ALT, ↑ AST, ↑ bilirubin (less common), ↑↑ **bile acids**. Associated with prematurity, intrauterine demise, and neonatal respiratory distress syndrome. Cholestasis resolves following delivery without hepatic sequelae
- **ACUTE FATTY LIVER OF PREGNANCY** (T3, incidence ~1 per 20,000 pregnancies)—may be associated with preeclampsia. Characterized by **severe liver dysfunction** (encephalopathy, hypoglycemia, coagulopathy) and commonly jaundice. ↑↑ ALT, ↑↑ AST, ↑ bilirubin, ↑ WBC, ↑ PT, ↑ **uric acid**. US is often normal (microvesicular fat on biopsy) and CT shows a low-density liver. May progress to acute hepatic failure and DIC in >75%. Increased maternal and fetal mortality

DIFFERENTIAL DIAGNOSIS (CONT'D)

PREGNANCY-AGGRAVATED LIVER DISEASE—hepatitis E, hepatitis A, HSV hepatitis, Budd-Chiari, cholelithiasis

- **HEPATITIS E**—may cause fulminant liver failure in pregnancy; mother to child transmission in 1/3 cases
- **HEPATITIS B**—pregnancy does **not** affect natural history of HBV infections (rare cases of fulminant hepatitis among immuncompro-

DIFFERENTIAL DIAGNOSIS (CONT'D)

mised). Routine screening at first prenatal visit (HBsAg). Prophylaxis and immunization for infant if mother HBV positive

- **HEPATITIS C**—pregnancy does **not** affect natural history of HCV infections. Mother to child transmission ~5% (up to 20% if HIV co-infection)
- **CHOLELITHIASIS**—associated with acute cholecystitis, choledocholithiasis, and ascending cholangitis
- **OTHER CONDITIONS**—drug-induced hepatitis, malignancy

CLINICAL FEATURES

HISTORY—jaundice, pruritus, abdominal pain, ascites, swelling, encephalopathy, nausea and vomiting, headache, visual disturbances, fever, obstetrical history (current pregnancy course, previous births, previous preeclampsia), past medical history (hypertension, hepatitis, alcohol, IDU), and medications

PHYSICAL—check vitals (hypertension), edema (facial, limbs), heart (elevated JVP, S3, S4), hepatic tenderness, ascites, jaundice, and hyperreflexia

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, lytes, urea, Cr, spot urine for protein to creatinine ratio, AST, ALT, ALP (mild elevation could be from placenta), GGT, bilirubin, INR, bile acids (intrahepatic cholestasis), uric acid (acute fatty liver), LDH, fibrinogen (DIC), TSH
- **MICROBIOLOGY**—HBV and HCV serology
- **IMAGING**—US abd

MANAGEMENT

HYPEREMESIS GRAVIDARUM—rule out molar pregnancy and hyperthyroidism. Consider alternative cause of N&V if persistent (adrenal insufficiency, eating disorder). Supportive fluids. Diclectin (doxylamine and pyridoxine) is first-line, then consider chlorpromazine, prochlorperazine, promethazine, metoclopramide, and ondansetron (in order of available fetal safety data)

MANAGEMENT (CONT'D)

INTRAHEPATIC CHOLESTASIS OF PREGNANCY—ursodeoxycholic acid 500 mg PO BID or cholestyramine for pruritus, increase fetal monitoring, consider early delivery as risk of fetal demise if high bile acids

ACUTE FATTY LIVER OF PREGNANCY—vitamin K if coagulopathic, early delivery. Can recur in future pregnancies

HELLP—anti-hypertensive, $MgSO_4$, early delivery

HEPATITIS B—provide standard neonatal immunoprophylaxis and consider antiviral treatment (tenofovir) if high maternal HBV DNA levels during pregnancy. Internal fetal monitoring and prolonged rupture of membranes should be avoided

HEPATITIS C—no proven treatment during pregnancy. Internal fetal monitoring and prolonged rupture of membranes should be avoided

SPECIFIC ENTITIES

OTHER GI DISORDERS

- **GERD**—very common during pregnancy. May cause chronic cough and reactive airway disease symptoms. Treatments include lifestyle changes, antacids, ranitidine, PPIs, and metoclopramide
- **CHOLECYSTITIS**—pregnant women are at increased risk due to hormonal changes. Medical management with IV fluids, NG, and opioids. Broad-spectrum antibiotics may be added for severe disease. Cholecystectomy safest during 2nd trimester

Related Topics
Acute Liver Failure (p. 143)
Dyspepsia (p. 125)

Infectious Diseases in Pregnancy

INFECTIONS ASSOCIATED WITH BIRTH DEFECTS

★**TORCHES CLLAP**★—**TO**xoplasma, **R**ubella, **C**MV, **H**SV, **E**nteroviruses, **S**yphilis, **C**hickenpox, **L**yme, **L**CMV, **A**IDS, **P**arvoviruses infections during pregnancy are associated with birth defects. Emerging data on many other potential pathogens that may also be associated with birth defects, such as *Brucella melitensis*, *Coxiella burnetii* (Q fever], *Babesia microti* (babesiosis), human T-cell lymphotropic virus types I and II, hepatitis G, TT viruses, human herpesvirus 6, and dengue

INFECTIONS ASSOCIATED WITH BIRTH DEFECTS (CONT'D)

SEPSIS

Common cause of maternal morbidity in developed and developing world. Assess vital signs (BP, HR, RR [tachypnea never normal], temperature), and for end-organ perfusion (level of consciousness, skin mottling), as well as for potential sources of infection. Medical management similar to treatment of sepsis in non-pregnant individuals with IV fluids and early empiric antibiotic therapy (see below for acceptable antibiotic choices)

INFLUENZA

Increased risk of influenza-related morbidity and mortality (5× higher risk of hospital admission overall, one out of six influenza-related deaths occur in young pregnant women). Influenza associated with adverse pregnancy outcomes (preterm birth, small for gestation age newborns). All pregnant women should receive inactivated influenza vaccine regardless of trimester

URINARY TRACT INFECTIONS

PATHOPHYSIOLOGY—hydronephrosis and hydroureter R > L, urinary stasis, higher protein and amino-acid excretion → UTI

ASYMPTOMATIC BACTERIURIA—defined as 10^5 CFU/mL on a "clean" sample. Occurs in 2–7% of pregnancies, associated with preterm birth, low birth weight, and perinatal mortality. Screen for bacteriuria between 12 and 16 weeks gestation, as 30–40% will develop symptomatic UTI if untreated. Treatment depends on culture and local antibiotic resistance pattern; consider *amoxicillin–clavulanate* 500 mg PO BID × 7 days, *nitrofurantoin* 100 mg PO BID × 7 days (risk of hemolytic anemia). Avoid trimethoprim if alternatives available. Follow-up culture 1 week following treatment completion and then monthly until pregnancy complete

ACUTE CYSTITIS—occurring in 1% of pregnancies, with treatment and follow-up as asymptomatic bacteriuria

PYELONEPHRITIS—occurring in <1% of pregnancies, complicated by septic shock and ARDS in 20%. In-patient treatment with IV antibiotics (cefazolin, ceftriaxone, or ampicillin plus gentamicin) until symptomatic improvement and afebrile for 24–48 h then PO based on drug sensitivities. Low-dose suppressive antibiotics (*nitrofurantoin* 50–100 mg PO qhs [risk of hemolytic anemia] or *cephalexin* 250–500 mg PO qhs) for remainder of pregnancy as recurrent pyelonephritis occurs in 6–8% of women without prophylaxis

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

ANTEPARTUM CARE—determine HIV symptoms, infections, immunization status, and perform ophthalmologic examination if CD4 <50/mm^3. Baseline testing include CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, CD4 count, viral load, genotype resistance assay, HLA-B*5701 (for abacavir), TB skin test, toxoplasma, VDRL, pap smear, cervical swabs for gonorrhea and chlamydia, CMV, HBV, and HCV serologies. All pregnant women with HIV should be treated with combination antiretroviral therapy (regardless of CD4 count or viral load), ideally with a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone that includes one or more NRTIs and a boosted protease inhibitor. If significant nausea, do not begin antiretroviral therapy until nausea is adequately controlled. Counsel regarding risk of perinatal transmission (<1% with consistent use of maternal combination antiretroviral therapy, intrapartum IV AZT, neonatal antiretroviral therapy × 6 weeks and avoiding breastfeeding). Prophylaxis for opportunistic infections same as in non-pregnant patients

INTRAPARTUM CARE—continue combination antiretroviral regimen during labor and delivery. Vaginal delivery recommended for women on antiretroviral therapy with viral load <1000 copies/mL (measured over last 4 weeks prior to delivery) in the absence of another specific obstetrical indication for cesarean section. Upon onset of labour or rupture of membranes, give *zidovudine* 2 mg/kg IV over 1 h, then 1 mg/kg/h until delivery (even if on HAART already). For cesarean section, start infusion at least 3 h before procedure. Consider cesarean delivery if viral load >1000 copies/mL. Avoid invasive monitoring, use of instruments to assist delivery, and prolonged interval between rupture of membranes and delivery

POSTPARTUM CARE—treat newborn with zidovudine for 6 weeks. Determine HIV status at birth, 4 weeks and 3–4 months with HIV RNA PCR. Avoid breast-feeding. Ensure good support system for mother. Counsel regarding contraceptive use

SOGC Guidelines for the Care of Pregnant Women Living With HIV 2014 J Obstet Gynaecol Can 2012;34:6

TUBERCULOSIS

MANAGEMENT—natural history not affected by pregnancy, but delayed recognition is common. Tuberculin skin testing and IFN-gamma release assays require expert interpretation in pregnancy.

TUBERCULOSIS (CONT'D)

Treat TB, if identified, as risk of infection to fetus is greater than risk of medications. Isoniazid, rifampin, and ethambutol safe for use during pregnancy and breastfeeding. *Pyridoxine* 25 mg PO daily is recommended for all pregnant or breastfeeding women taking isoniazid to prevent peripheral neuropathy

ANTIBIOTICS

ACCEPTABLE—penicillins, cephalosporins, azithromycin, vancomycin, metronidazole, clindamycin, erythromycin (except erythromycin estolate), nitrofurantoin (caution as risk of hemolytic anemia), and acyclovir. Consider trimethoprim–sulfamethoxazole (avoid in first trimester but use with folate if no other alternatives) and aminoglycosides (except streptomycin) in some circumstances

ANTIBIOTICS (CONT'D)

AVOID—tetracyclines (infant teeth staining), streptomycin (theoretical concern for fetal ototoxicity), fluoroquinolones (abnormal cartilage development in animals, but not demonstrated in humans)

Related Topics
HIV (p. 291)
Tuberculosis (p. 279)
Urinary Tract Infections (p. 272)

Diabetes in Pregnancy Canadian Diabetes Association 2013 Guidelines

PATHOPHYSIOLOGY

RISK FACTORS FOR GESTATIONAL DIABETES—previous history of gestational diabetes, impaired fasting glucose or impaired glucose intolerance, prior delivery of macrosomic infant or current fetal macrosomia (>4000 g or >90th percentile), polyhydramnios, high-risk ethnic group (Aboriginal, Hispanic, South Asian, Asian, African), maternal age ≥35, obesity (BMI ≥30 kg/m^2), corticosteroid use, PCOS, acanthosis nigricans

PRECONCEPTION CARE FOR PREGESTATIONAL DIABETES—for preexisting diabetes (type 1 or 2), optimize glycemic control prior to pregnancy (HbA1c ≤7%) and suggest weight reduction (if overweight). Screen for retinopathy and nephropathy. Patients on oral agents should switch to insulin for glycemic control. Discontinue ACE inhibitors, ARBs, and statins prior to conception (or immediately upon detection of pregnancy). Supplemental *folic acid* 5 mg PO daily starting at least 3 months preconception until at least 12 weeks gestation, then 0.4–1 mg PO daily

DIAGNOSIS

DIAGNOSIS OF GESTATIONAL DIABETES—screen all pregnant women between 24–28 weeks, or additionally at any stage of pregnancy if at high risk of gestational diabetes (see risk factors above):

- **Step 1: 1-h 50 g oral glucose tolerance test (non-fasting)**
  - If 1 h blood glucose ≥11.1 mmol/L [≥200 mg/dL] → GDM
  - If 1 h blood, glucose 7.8–11.0 mmol/L [140–200 mg/dL] → perform 75 g OGTT
  - If 1 h blood glucose <7.8 mmol/L [<140 mg/dL] → no GDM, but may consider re-testing if ongoing suspicion (e.g., macrosomia, polyhydramnios)
- **Step 2 (if needed): 2-h 75 g oral glucose tolerance test (fasting)**
  - If fasting blood glucose ≥5.3 mmol/L [≥95 mg/dL] → GDM
  - If 1 h blood glucose ≥10.6 mmol/L [≥190 mg/dL] → GDM
  - If 2 h blood glucose ≥9.0 mmol/L [≥160 mg/dL] → GDM

MANAGEMENT

ANTEPARTUM—diabetic diet and exercise. Aim for excellent glycemic control with HbA1C <7% prior to and throughout pregnancy. Monitor blood glucose before and after each meal. Target fasting blood glucose <5.3 mmol/L [<95 mg/dL] and 2 h postprandial blood glucose <6.7 mmol/L [<120 mg/dL] (modify targets if hypoglycemia occurs). Test urine for ketones during illness, or if patient suspected of over-restricting diet (starvation) in order to achieve tight glycemic control. Monitor blood pressure at each visit. In patients with preexisting diabetes (type 1 or 2), screen for retinopathy (ophthalmologist) and nephropathy (serum creatinine and urine albumin/Cr ratio)

- **GESTATIONAL DIABETES**—dietician referral. If glycemic targets not achieved within 1–2 weeks, start insulin (lispo or aspart SC ac meals, and/or NPH

MANAGEMENT (CONT'D)

SC QHS–BID). Adjust dose weekly, as needed. Consider glyburide or metformin for women non-adherent to or who refuse insulin (off-label use in pregnancy, discuss risks with patient)

- **TYPE 1 DIABETES**—basal-bolus insulin therapy or insulin pump
- **TYPE 2 DIABETES**—switch from oral agents to insulin, preferably preconception (lispo or aspart SC ac meals, and/or NPH SC QHS–BID). Adjust dose weekly, as needed. Consider glyburide or metformin for women non-adherent to or who refuse insulin (off-label use in pregnancy, discuss risks with patient)

INTRAPARTUM—target blood glucose 4.0–7.0 mmol/L [72–126 mg/dL] during labor (to minimize risk of neonatal hypoglycemia). NPO, IV fluids, and monitor blood glucose q1h. Consider insulin IV infusion (rarely required for GDM), according to current blood glucose level, time of last meal, and time of last insulin injection

POSTPARTUM—insulin requirements rapidly drop after delivery, especially if breastfeeding (beware of hypoglycemia). Breastfeeding should be encouraged to reduce risk of neonatal hypoglycemia, offspring obesity, and metabolic syndrome in mother

MANAGEMENT (CONT'D)

- **GESTATIONAL DIABETES**—insulin rarely required postpartum. Risk of type 2 diabetes (20% in 10 years); screen from 6 weeks to 6 months postpartum with 2 h 75 g OGTT
- **TYPE 1 DIABETES**—reduce insulin (using preconception dosages as guideline). Screen for postpartum thyroiditis 6–8 weeks postpartum with TSH
- **TYPE 2 DIABETES**—reduce or discontinue insulin (using preconception dosages as guideline). Metformin and glyburide safe while breastfeeding

COMPLICATIONS—fetal complications include congenital anomalies (usually with preexisting diabetes), macrosomia (shoulder dystocia, birth trauma) or intrauterine growth restriction (uncommon), neonatal hypoglycemia, respiratory distress syndrome, hypocalcemia, hyperbilirubinemia, and intrauterine death. Offspring at risk for diabetes and obesity in long-term. Maternal complications include gestational hypertension, preeclampsia, polyhydramnios, preterm labor (C-section), and progression of diabetic retinopathy and nephropathy

Can J Diabetes 2013 37:S168-S183

Thyroid Diseases in Pregnancy

HYPOTHYROIDISM IN PREGNANCY

PATHOPHYSIOLOGY—hypothyroidism, when present, usually diagnosed prior to conception (most commonly Hashimoto's). Around 75% of women will require an increase in levothyroxine during pregnancy. ↑ estrogen → ↑ thyroxine-binding globulin → ↓ total T4 and total T3. Estimated required increase in T4 to maintain euthyroidism is 25–50%. Hypothyroidism may also be diagnosed in pregnancy (uncommon). ↑ thyroid hormone synthesis and ↑ renal clearance of iodine → ↑ iodine requirements during pregnancy, but if iodine intake insufficient (endemic) → ↓ T4 and ↑ TSH

MONITORING—screen high risk individuals (history of goiter, thyroid dysfunction, thyroid ablation, thyroidectomy, neck irradiation, autoimmune conditions, family history). Preconception, target TSH 0.2–2.5 mU/L (lower normal range). In T_1, target TSH 0.1–2.5 mU/L (and free T4 in upper normal range); T_2, target TSH 0.2–3 mU/L (and *total* T4 in normal of *pregnancy-adjusted* range); and T_3, target TSH 0.3–3 mU/L

HYPOTHYROIDISM IN PREGNANCY (CONT'D)

(and *total* T4 in normal of *pregnancy-adjusted* range). Use FT4 in first trimester and *total* T4 in second/third trimesters. Monitor TSH and free T4 (or total T4) levels q4weeks during first half of pregnancy and at least once between 26 and 32 weeks' gestation

TREATMENTS—levothyroxine can be safely given during pregnancy. As soon pregnancy is confirmed, ↑ dose by 30% empirically. Levothyroxine should be taken separate from vitamins and ideally on an empty stomach to ensure best absorption

COMPLICATIONS—untreated hypothyroidism associated with neonatal neuropsychological and cognitive impairment, preeclampsia and gestational hypertension, preterm labor, placental abruption, and perinatal morbidity and mortality

HYPERTHYROIDISM IN PREGNANCY

PATHOPHYSIOLOGY—most commonly Graves' disease. TSH receptor stimulating antibody → ↑ thyroid hormone production. Hyperthyroidism

HYPERTHYROIDISM IN PREGNANCY (CONT'D)

may also arise from excess hCG (self-limited surge in T_1 [transient gestational thyrotoxicosis], multiple gestation, hyperemesis gravidarum, or molar pregnancy [hydatidiform mole]) → hCG α-subunit identical to TSH α-subunit → ↑ thyroid hormone production → ↓ TSH

COMPLICATIONS—preeclampsia, premature labor, placental abruption, intrauterine growth restriction, fetal goiter (from excess antithyroid drug treatment), neonatal thyrotoxicosis (typically when TSH receptor antibodies >3–5× upper limit of normal), ↑ mortality (maternal and perinatal), and thyroid storm (rare)

SUBCLINICAL HYPERTHYROIDISM—not associated with adverse outcomes. Supportive care, reassurance, and postpartum follow-up

EXCESS hCG EFFECT—transient gestational thyrotoxicosis may be present in 5–10% of pregnancies during T_1 (↓ TSH, normal/slightly ↑ FT4). Self-limited and typically resolves by T_2. Treatment is supportive with reassurance

GRAVES' DISEASE—most common cause of primary hyperthyroidism in pregnancy (95%). TSH receptor antibodies can cross placenta to cause fetal thyrotoxicosis. Classically improves in pregnancy. Exacerbations may happen in T_1 and postpartum

- **DIAGNOSIS**—presence of symptoms predating pregnancy, eye signs, weight loss despite adequate intake, and pretibial myxedema suggestive of Graves' disease. However, presence of mild–moderately enlarged thyroid gland, hypervascularity, and/or nodularity usually unhelpful in differentiating between Graves' disease vs. normal physiological changes. Presence of ↑ TSH receptor antibodies suggests Graves' disease. Nuclear imaging contraindicated in pregnancy. Postpartum course can also help clarify etiology
- **MONITORING**—in T_1, target TSH 0.1–2.5 mU/L (and free T4 in upper normal range); T_2, target TSH 0.2–3 mU/L (and *total* T4 in normal *pregnancy-adjusted* range); and T_3, target TSH 0.3–3 mU/L (and *total* T4 in normal *pregnancy-adjusted* range). Use FT4 in first trimester and *total* T4 in second/third trimesters. Monitor TSH and free T4 (or total T4) levels q4weeks
- **TREATMENT**—***antithyroid drugs***, preferably *propylthiouracil* during T_1 and methimazole during T_2-T_3 (propylthiouracil associated with idiosyncratic liver injury, methimazole associated with aplasia cutis). Mild under-treatment preferred to hypothyroidism. May require lower dosages of antithyroid medication as pregnancy progresses. Taper or discontinue medication, if possible, towards delivery date to decrease risk of neonatal goiter. ***β-blockers*** (prefer *propranolol*; avoid atenolol) for symptom control, but may lead to fetal bradycardia, fetal hypoglycemia, and intrauterine growth restriction at higher doses. Avoid radioiodine during pregnancy. If surgery required (rare), ideally during T_2. Consult high-risk obstetrician, to monitor maternal and fetal health

POSTPARTUM THYROIDITIS—painless (silent) and affects 10% of postpartum women within first postpartum year (usually first 3–6 months) and may be associated with postpartum depression. Classically begins with a hyperthyroid phase followed by hypothyroid phase. Only 25% have hypothyroid phase. Most cases resolve within 1 year. Risk of recurrence is up to 25% in subsequent pregnancies. Approximately 20–40% go on to develop permanent hypothyroidism

- **TREATMENT**—most patients have mild thyrotoxicosis (×1–2 months) and do not require treatment. For symptomatic thyrotoxicosis give β-blocker. Most eventually return to euthyroid state, but some become hypothyroid. If levothyroxine is needed, start 50–100 μg PO daily, and slowly withdraw after around 6 months as hypothyroidism may have resolved. Monitor TSH q6–8 weeks

Other Disorders in Pregnancy

SEIZURES IN PREGNANCY

PATHOPHYSIOLOGY—for women with known epilepsy, 25% will have ↑ frequency (secondary to non-adherence or inappropriately low antiepileptic drug levels), 25% will have ↓ frequency, and 50% will not change in pregnancy. Risk of uncontrolled seizures in pregnancy outweighs risks of antiepileptic drugs. Risk of seizures in offspring is elevated at 5%. Eclampsia, intracerebral bleed, and cerebral vein thrombosis may lead to seizures in pregnancy

TREATMENTS—valproic acid has a relatively high risk of neural tube defects and should be switched to alternate antiepileptic pre-pregnancy

SEIZURES IN PREGNANCY (CONT'D)

if possible. Phenytoin, carbamazepine, and phenobarbital are potentially teratogenic (especially if polytherapy required) but can be used if indicated and after appropriate counseling. Lamotrigine seems to have reasonable data in pregnancy. *Folic acid* 0.4 mg PO daily should be prescribed to all women on antiepileptics in the childbearing age. Those planning a pregnancy should take *folic acid* 5 mg PO daily in the preconception period and in first trimester, then 1 mg PO daily throughout remainder of pregnancy

LUPUS IN PREGNANCY

LUPUS EXACERBATIONS—may have increased flares during pregnancy and postpartum if not in remission for >6 months prior to conception. Plaquenil, azathioprine, and corticosteroids may be used during pregnancy. Avoid NSAIDs in T_3

COMPLICATIONS—increased risk of prematurity and in utero fetal death. Patients with nephritis may have severe exacerbations with acute renal failure, preeclampsia, and maternal death. Test for maternal anti-SSA and anti-SSB antibodies (associated with increased risk of congenital heart block and neonatal lupus) and monitor fetus with fetal heart rate and echocardiogram between 18 and 26 weeks gestation. Patients with antiphospholipid antibodies are at increased risk of preeclampsia, miscarriage, and possibly thrombosis

BREAST CANCER IN PREGNANCY

DIAGNOSIS—often delayed given physiological changes. Staging workup similar to non-pregnant women. Use MRI or US instead of CT if imaging of abdomen required

TREATMENTS—mastectomy preferred over lumpectomy to avoid radiation. If adjuvant radiation indicated, it should be deferred until after delivery. Anthracycline containing adjuvant chemotherapy can usually be safely given during T_2 and T_3, but not in T_1 or within 2 weeks of delivery. Methotrexate is absolutely contraindicated and taxane/dose dense regimens should be avoided. Hormonal therapy is contraindicated during pregnancy. Breast-feeding contraindicated in women on hormonal therapy or chemotherapy. Stage by stage, gestational breast cancer has similar prognosis to non-pregnant counterpart

PAIN CONTROL IN PREGNANCY

ACCEPTABLE—acetaminophen, opioids

WITH CAUTION—NSAIDs in T_1 and T_2

PAIN CONTROL IN PREGNANCY (CONT'D)

CONTRAINDICATED—NSAIDs in T_3 (premature closure of ductus arteriosus, fetal renal insufficiency, and periventricular hemorrhage)

THROMBOCYTOPENIA IN PREGNANCY

PERIPARTUM CONSIDERATIONS—neuraxial anesthesia (epidural) generally safe if platelet $>75\times10^9$/L; Cesarean delivery safe if platelet $>50\times10^9$/L; vaginal delivery safe if platelets $>30\times10^9$/L

GESTATIONAL THROMBOCYTOPENIA (T_3)—asymptomatic and resolves rapidly after pregnancy. May be difficult to distinguish from ITP initially (until postpartum). Platelet count usually higher ($>70\times10^9$/L) in gestational thrombocytopenia. Follow platelet count q4weeks initially then q1week after 36th week

ITP (T_1–T_3)—may use prednisone and IVIG in pregnancy. Platelet transfusion if acute. Monitor closely. Splenectomy is last resort (safest in T_2). 10% of newborns may also develop thrombocytopenia due to placental transfer of maternal antibodies, but intracranial hemorrhage rare (<1%). Maternal platelet count does not predict fetal platelet count. Fetal platelet counts should be tested and monitored, as needed, after birth

PREECLAMPSIA/HELLP (T_2–T_3)—supportive, early delivery, steroids for lung maturity if delivered <34 weeks (see earlier sections)

TTP/HUS—presence of severe thrombocytopenia and microangiopathic hemolytic anemia (↑↑↑ LDH) differentiates TTP/HUS from HELLP. Requires plasma exchange ± dialysis

OTHERS—DIC, nutritional deficiencies (vitamin B12, folic acid), HIV, hepatitis B and C, drugs, autoimmune diseases (APLA), hypersplenism, and primary bone marrow disorders

ANTIPHOSPHOLIPID ANTIBODY SYNDROME IN PREGNANCY

PATHOPHYSIOLOGY—persistent presence of antibody against phospholipids or cell surface proteins bound to anionic phospholipids. These include lupus anticoagulants (associated with thrombotic events), anticardiolipin antibody (associated with thrombotic events and obstetric complications; false-positive VDRL), and anti-β2GP1 antibody → most lead to hypercoagulable state, some may inhibit coagulation. Higher risk associated with higher antibody titer

CLINICAL FEATURES—venous and arterial thrombosis and rarely hemorrhage affecting the lungs, heart, CNS, GI, kidneys, skin, and eyes. Also

ANTIPHOSPHOLIPID ANTIBODY SYNDROME IN PREGNANCY (CONT'D)

thrombocytopenia (via ITP, TTP), Raynaud's phenomenon, ↑ risk of preeclampsia/eclampsia, recurrent fetal losses (see below), and intrauterine growth restriction

CAUSES—primary APS, secondary APS (various rheumatic diseases such as SLE, infections such as HIV and drugs)

DIAGNOSIS—clinical criteria of VTE or arterial thrombosis, or ≥3 unexplained losses <10 weeks, or ≥1 unexplained loss of morphologically normal fetus ≥10 weeks, or ≥1 premature births <34 weeks because of preeclampsia/eclampsia/placental insufficiency; *plus* laboratory criteria of elevated anticardiolipin antibodies, or lupus anticoagulant, or anti-β2GP1 antibodies, confirmed >12 weeks apart. Diagnosis requires at least one clinical and one laboratory criteria

ANTIPHOSPHOLIPID ANTIBODY SYNDROME IN PREGNANCY (CONT'D)

TREATMENTS—for women with APS associated with adverse obstetric outcomes, give prophylactic LMWH and low-dose ASA during pregnancy. For women with APS associated with VTE, same antenatal treatment plus anticoagulation prophylaxis postpartum for 6 weeks (see p. 175 for more details on ANTIPHOSPHOLIPID ANTIBODY SYNDROME)

Related Topics

Antiphospholipid Antibody Syndrome (p. 175)
Breast Cancer (p. 208)
Lupus (p. 316)
Thrombocytopenia (p. 167)
Seizures (p. 350)

17

GENERAL INTERNAL MEDICINE

Christopher Ma and Peter Hamilton

Approach to Diagnostic Tests and Clinical Trials

DIAGNOSTIC TESTS

2×2 TABLE

	Disease present	Disease absent	Total
Test positive	*a* (true positive)	*b* (false positive)	*a*+*b*
Test negative	*c* (false negative)	*d* (true negative)	*c*+*d*
Total	*a*+*c*	*b*+*d*	*a*+*b*+*c*+*d*

SENSITIVITY ★SNOUT★
- = *a*/(*a*+*c*)
- = out of 100 patients with disease, how many have a positive test result? Independent of prevalence and helps to rule **out** disease

SPECIFICITY ★SPIN★
- = *d*/(*b*+*d*)
- = out of 100 people without disease, how many have a negative test result? Independent of prevalence and helps to rule **in** disease

POSITIVE PREDICTIVE VALUE (PPV)
- = *a*/(*a*+*b*)
- = out of 100 patients with a positive test result, how many actually have disease? Dependent on prevalence of disease

NEGATIVE PREDICTIVE VALUE (NPV)
- = *d*/(*c*+*d*)
- = out of 100 patients with a negative test result, how many do not have disease? Dependent on prevalence of disease

LIKELIHOOD RATIOS (LR)—indicates how much a given diagnostic test result will change the pretest probability of the disorder under investigation:
- LR 1.0 means pre-test probability = post-test probability

DIAGNOSTIC TESTS (CONT'D)

- LR >1.0 increases the probability the disorder is present. A test with LR >10 is particularly useful
- LR <1.0 decreases the probability the disorder is present. A test with LR <0.1 is particularly useful

POSITIVE LIKELIHOOD RATIO (LR+)
- = (positive test in disease)/(positive test in no disease)
- = sensitivity/(1 – specificity)

NEGATIVE LIKELIHOOD RATIO (LR–)
- = (negative test in disease)/(negative test in no disease)
- = (1 – sensitivity)/specificity

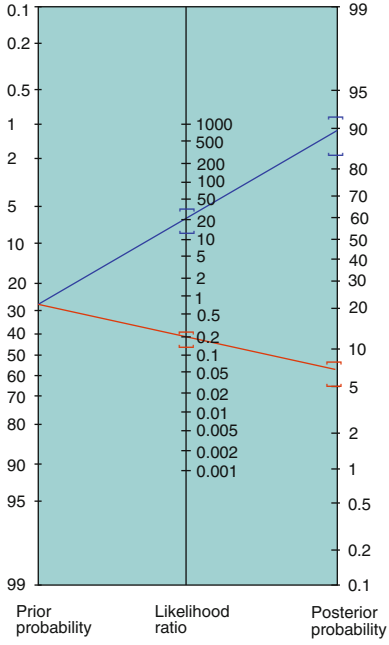
ACCURACY
- = (*a*+*d*)/(*a*+*b*+*c*+*d*)
- = how often is test correct in predicting true positive and true negative

TO CALCULATE THE POST-TEST PROBABILITY OF A DIAGNOSIS AFTER A TEST
- **PRE-TEST PROBABILITY**
  - = probability of disease just prior to performing test of interest
  - = disease prevalence (if no other diagnostic test previously performed) or post-test probability (after other initial investigations)
- **PRE-TEST ODDS** = pre-test probability/(1 – pre-test probability)
- **POST-TEST ODDS** = pre-test odds × likelihood ratio
- **POST TEST PROBABILITY** = (post-test odds)/(1 + posttest odds)

FAGAN NOMOGRAM—easily converts from pre-test probability to post-test probability using LR (alleviating tedious calculations above)

D. Hui et al. (eds.), *Approach to Internal Medicine: A Resource Book for Clinical Practice*,
DOI 10.1007/978-3-319-11821-5_17, © Springer International Publishing Switzerland 2016

DIAGNOSTIC TESTS (CONT'D)



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THERAPEUTIC INTERVENTIONS

2×2 TABLE

	Outcome positive	Outcome negative	Total
Exposure positive	*A*	*B*	$a+b$
Exposure negative	*C*	*D*	$c+d$
Total	$a+c$	$b+d$	$a+b+c+d$

ODDS RATIO (OR)
– case control study
= ad/bc. Odds ratio approximates RR if the disease is relatively rare

RELATIVE RISK (RR)
– cohort study
= $[a/(a+b)]/[c/(c+d)]$
= probability of disease in exposed patients/probability of disease in patients without exposure

RELATIVE RISK REDUCTION (RRR)

$= [a/(a+b) - c/(c+d)]/[c/(c+d)]$

ABSOLUTE RISK REDUCTION (ARR)

$= a/(a+b) - c/(c+d)$

NUMBER NEEDED TO TREAT (NNT)
=1/ARR = number of patients you would need to treat for one patient to benefit from the treatment of interest

Smoking Cessation NEJM 2002 346:7; NEJM 2008 359:19

COMPLICATIONS AND SMOKING-ASSOCIATED DISORDERS

CANCER—lung, head and neck (larynx, pharynx, oral cavity), esophagus, pancreas, bladder, kidney, stomach, cervix, AML

CARDIOVASCULAR DISEASES—CAD, CVD, PVD, Buerger's disease

RESPIRATORY DISEASES—COPD, pneumonia

METABOLIC—diabetes mellitus, infertility, premature menopause, osteoporosis

COAGULOPATHY

MORTALITY—all-cause mortality ~3-fold higher (death most commonly from neoplastic, vascular or respiratory causes)

PATHOPHYSIOLOGY OF SMOKING

NICOTINE ADDICTION—related to the combination of the following: (1) the pleasurable effects of nicotine (e.g. relief of anxiety and arousal); (2) the pleasurable effects of associated environmental triggers (e.g. coffee and meals); and (3) the unpleasureable effects of nicotine withdrawal (e.g. dysphoria, anxiety, irritability, insomnia, decreased concentration, increased appetite and over the long-term increased weight)

LUNG CANCER—cigarette smoke contains numerous carcinogenic substances. In particular, *N*-nitrosamines and polycyclic aromatic hydrocarbons are metabolized to nitrosamine ketone and

PATHOPHYSIOLOGY OF SMOKING (CONT'D)

N'-nitroso-nornicotine by the cytochrome P450 system, which form DNA adducts, leading to mutations and eventually cancer. The duration of cigarette exposure is a greater risk factor than the number of cigarettes smoked per day. Cigarette smoking is a greater risk factor than pipe and cigar smoking. Smokers have a 10–30× increased risk of developing lung cancer. The risk the lung cancer returns close to baseline (i.e. 80–90% reduction) after 10–15 years of smoking cessation. Second-hand smokers have up to 2× increased risk of lung cancer

LIFE EXPECTANCY—on average, 13.2 and 14.5 years shorter for male and female smokers compared to non-smokers, respectively. Smoking cessation between 45 and 54 years of age reduces risk of death associated with continued smoking by two-thirds.

MANAGEMENT OF SMOKING CESSATION

COUNSELING—identify smoking cues and use cognitive and behavioral methods to break the link. **Remove cues** (remove ash trays, avoid settings where smoking occurs, suggest other smokers in the household to quit at the same time, or other substances). **Coping** (inform family/friends/co-workers about quitting and seek support, plan strategies such as gum, stress management)

DRUG THERAPY—**nicotine replacement** (nicotine gum, *nicotine transdermal* 21 mg daily×6 weeks, then 14 mg daily×2 weeks, then 7 mg daily×2 weeks). ***Bupropion SR*** (150 mg PO daily×3 days, then BID×7–12 weeks, stop smoking after 6–7 days of treatment). **Nicotinic acetylcholine receptor partial agonist** (*varenicline* 0.5 mg PO daily for d1–3, then 0.5 mg PO BID d4–7, then 1 mg PO BID for weeks 2–12). E-cigarettes/personal vaporizers may assist with abstinence but are not currently FDA-approved for smoking cessation

TREATMENT ISSUES

APPROACH TO COUNSELING

1. **SCREENING**—identification of smokers at every visit and explore willingness to quit
2. **EXPLORE PATIENT'S OWN REASONS TO QUIT**—current health, social (e.g. children), or economic issues. Explain comorbidities associated with smoking. "As your doctor, I need you to know that quitting smoking is the most important thing you can do to protect your health"
3. **IF PATIENT READY TO QUIT WITHIN 30 DAYS**—offer counseling (quit date, what worked, what did not, express confidence, strategies) and aid (nicotine replacement, bupropion)
4. **IF PATIENT WANTS TO QUIT BUT NOT NOW**—explore barriers to smoking cessation (nicotine dependence, fear of failure, lack of social support, lack of self-confidence, concern about weight gain, depression, substance abuse). Explore reasons to quit (health, social, financial). Set quit date. Follow-up
5. **IF PATIENT NOT READY TO QUIT**—avoid argument. Explore smoker's view of pros/cons of smoking and cessation and correct misperceptions. Discuss risks of passive smoking for family and friends. Advise no-smoking policy at home. Offer to help the smoker when ready to quit

OBSTACLES TO CESSATION

- **WEIGHT GAIN AFTER CESSATION**—2.3–4.5 kg [5–10 lb]
- **PHYSIOLOGICAL**—withdrawal symptoms (see pathophysiology) usually begin few hours after the last cigarette, peak 2–3 days later, and wane over several weeks
- **PSYCHOLOGICAL**—smoking is a learned behavior/ritual. High risk of relapse (40% at 5 years); requires clinical follow-up

SIDE EFFECTS OF SMOKING CESSATION METHODS

- **NICOTINE GUM**—mouth irritation, sore jaw, dyspepsia, hiccups, and damage to dental work
- **NICOTINE PATCH**—skin irritation and insomnia. Contraindications include unstable angina or MI <2 weeks, pheochromocytoma (increases catecholamine release) and pregnancy
- **BUPROPION SR**—discontinuation rate of around 10%. Insomnia, dry mouth, agitation, increased risk of seizure <0.1%. May increase the risk of suicide. Enters breast milk
- **VARENICLINE**—dose-related nausea and vomiting. Insomnia, abnormal dreams, headaches, constipation, diarrhea, flatulence, and dyspepsia. Contraindicated in pregnancy. Use with CAUTION in mood disorders as may increase suicidal ideation

PROGNOSTIC ISSUES

CESSATION RATE

- **WITHOUT HELP**— <10%
- **COMBINE DRUG THERAPY WITH COUNSELING**—40–60% at the end of drug treatment, 25–30% at 1 year. The use of drug therapy (either nicotine replacement or bupropion) increases success rate by 2–3× compared to placebo

Related Topics
Coronary Artery Disease (p. 28)
Esophageal cancer (p. 215)
Lung cancer (p. 203)

Multisystem Disorders

SELECTED MULTISYSTEM DISORDERS

INFECTIONS
- **BACTERIAL**—endocarditis, TB, Whipple's
- **VIRAL**—HIV, HBV, HCV, EBV, CMV
- **FUNGAL**—histoplasmosis, aspergillosis
- **PARASITIC**—schistosomiasis

MALIGNANCY
- **SOLID**—metastatic, paraneoplastic
- **LYMPHOPROLIFERATIVE**—leukemia, lymphoma

INFLAMMATORY—vasculitis, rheumatoid arthritis, scleroderma, SLE, IBD
IATROGENIC—drugs
INFILTRATIVE—cryoglobulinemia, hemochromatosis, amyloidosis, sarcoidosis, porphyria
ENDOCRINE—diabetes, hyperthyroidism

HEMOCHROMATOSIS

INHERITANCE—autosomal recessive. Among the North American population of European descent, approximately 10% are heterozygous and 0.4% are homozygous for hemochromatosis
PATHOPHYSIOLOGY—mutation of HFE gene (C282Y and H63D most common mutations); normally forms a complex with transferrin receptor to decrease its affinity for transferrin → mutation causes ↑ absorption of Fe → iron deposition in organs
CLINICAL FEATURES—**skin** (bronze), **joints** (destructive arthritis, classically 2nd and 3rd MCP), **heart** (arrhythmia, heart failure), **pancreas** ("bronze" diabetes), **thyroid** (hypothyroidism), **liver** (↑ LFT, cirrhosis, hepatocellular carcinoma 200× ↑ risk, cholangiocarcinoma rare), **gonads** (hypogonadism, impotence), **pituitary** (hypopituitarism), **infections** (*Listeria*, *Yersinia*, *Vibrio*)
DIAGNOSIS—transferrin % saturation (=serum iron/TIBC × 100%, ↑, most useful for screening), Fe (↑), TIBC, ferritin (↑), liver biopsy (hepatic iron index), HFE genotype testing
TREATMENTS—**alcohol cessation**, **phlebotomy** (remove 1–2 U weekly until ferritin <50 ng/mL). Chelation only if phlebotomy contraindicated (e.g. moderate/severe anemia) or not tolerated (e.g. hypotension)

Lancet 2007 370:9602

SARCOIDOSIS

PATHOPHYSIOLOGY—cause unknown but may involve antigen exposure → activation of T-cell immunity → non-caseating granuloma formation
CLINICAL FEATURES—**constitutional** (fatigue, weight loss, fever), **pulmonary** (staged according to CXR: stage I = bilateral hilar adenopathy, stage II = hilar adenopathy with parenchymal reticular opacities, upper > lower, stage III = parenchymal reticular opacities without hilar adenopathy, stage IV = advanced fibrosis with evidence of volume loss, honey-combing, hilar retraction, bullae, cysts, and emphysema. Stages not necessarily chronological), **cardiac** (arrhythmia especially conduction blocks, HF), **GI tract** (hepatomegaly, rarely ulcers, obstruction), **renal** (interstitial nephritis, nephrocalcinosis), **neurologic** (cranial nerve palsies especially CN VII, pituitary dysfunction, peripheral neuropathy, neuromuscular, transverse myelitis), **ocular** (uveitis), **endocrine** (hypercalcemia, hypopituitarism), **lymphatics** (lymphadenopathy, hypersplenism), **joints/bone** (symmetrical acute polyarthritis of ankles, chronic arthritis of large or small joints of hands and feet, bone pain with periosteal resorption), and **skin** (erythema nodosum, lupus pernio). **Lofgren's syndrome** is an acute presentation characterized by bilateral hilar lymphadenopathy, erythema nodosum, arthritis, fever, ±uveitis (50%). It is associated with a good prognosis with >80% remission in 2 years
INVESTIGATIONS—**blood tests** (CBCD, lytes, urea, Cr, Ca, PO_4, AST, ALT, ALP, bilirubin, serum ACE level), **urine tests** (urinalysis), **imaging** (CXR, high resolution CT chest), **special** (TB skin test, ECG, PFT, LP if neurological symptoms, BAL, biopsy, ophthalmology referral). Diagnosis is made by clinical findings plus biopsy (except if Lofgren's syndrome)
PROGNOSIS—poor prognostic factors include age at onset >40, black race, progressive pulmonary sarcoidosis, neurological or cardiac involvement, chronic uveitis, lupus pernio, chronic hypercalcemia, and nephrocalcinosis
TREATMENTS
- **LUNG INVOLVEMENT**—observation only if asymptomatic, minimal parenchymal changes, Lofgren's syndrome, or stage I lung disease as high chance of spontaneous remission. Inhaled steroids for mild disease (*budesonide* 800–1600 mcg BID × 4–8 weeks) and systemic steroid (*prednisone* 1 mg/kg PO daily × 4–6 weeks) for moderate/severe disease
- **SKIN AND EYE INVOLVEMENT**—topical steroid
- **JOINT INVOLVEMENT**—NSAIDs/colchicine
- **CARDIAC OR NEUROLOGIC INVOLVEMENT OR ANY OTHER PROGRESSIVE DISEASE**—*prednisone* 0.5–1 mg/kg PO daily, methotrexate, azathioprine, cyclophosphamide and infliximab

Lancet 2014 383:9923

AMYLOIDOSIS

PATHOPHYSIOLOGY—soluble amyloid precursor protein (AL = Ig light chain variable region in plasma cell dyscrasias, AA = serum amyloid A in chronic inflammatory conditions, ATTR = derived from mutant transthyretin protein, Aβ = Aβ protein precursor in Alzheimer's, β2-microglobulin in advanced chronic kidney disease/chronic hemodialysis) → insoluble fibrils in anti-parallel β-pleated sheet configuration → deposition in different organs

CLINICAL FEATURES—**constitutional** (fatigue, weight loss), **renal** (nephrotic proteinuria, distal RTA, nephrogenic diabetes insipidus), **cardiac** (HF, cardiomyopathy, arrhythmia, heart block, MI), **neurologic** (mixed sensory/motor peripheral neuropathy, autonomic neuropathy, bowel/bladder dysfunction, intracranial bleeding), **pulmonary** (pleural effusion, parenchymal nodules, tracheobronchial infiltration), **GI tract** (GI bleed, malabsorption, pseudoobstruction/dysmotility), **hepatic** (hepatomegaly), **hematologic** (bruising, factor X deficiency, binding of Ca-dependent factors to amyloid), **endocrine** (adrenal insufficiency, hypothyroidism), **soft tissues** (muscle pseudohypertrophy, shoulder pad sign, nail dystrophy, alopecia, macroglossia which is specific to AL, occurring in 20%)

DIAGNOSIS—serum and urine protein electrophoresis, biopsy of involved organ, subcutaneous fat, rectal tissue, and bone marrow biopsy. Immunofixation electrophoresis (AL), immunohistochemical staining for specific amyloid protein (AA). Amyloid stains red with Congo red dye and shows "apple-green" birefringence under polarized light

PROGNOSIS—median survival is 1–2 years for AL, but only 6 months if cardiac involvement. Up to 15 years in ATTR. Prognosis is dependent on underlying disease in AA

TREATMENTS—supportive (dialysis if renal failure). Treatment of underlying infectious/inflammatory disorder (AA) and plasma cell dyscrasia (AL)

NOTE—amyloidosis usually involves *λ* light chain, whereas light chain deposition disease involves *κ* light chain

NEJM 1997 337:13

CRYOGLOBULINEMIA

PATHOPHYSIOLOGY—chronic immune stimulation or lymphoproliferation resulting in production of immunoglobulin (mono- or polyclonal), i.e. cryoglobulin (type I = monoclonal IgG/IgM/IgA/free light chains, produced by Waldenstrom's macroglobulinemia/myeloma/lymphoproliferative disorder; type II = monoclonal IgM/IgA against polyclonal Ig, may be essential or due to persistent viral infections [HCV/HIV]; type III = polyclonal Ig against polyclonal Ig, may be essential or due to connective tissue diseases) → cryoglobulin precipitates with complexes at temperature <37 °C [<98.6 °F] → hyperviscosity and deposition in organs/vessels → systemic inflammation/vasculitis

CLINICAL FEATURES OF TYPE I—**skin** (livedo reticularis, purpura), **hyperviscosity/thrombosis** (Raynaud's phenomenon, digital ischemia)

CLINICAL FEATURES OF TYPE II/III—**constitutional** (fatigue, weight loss, arthralgia, myalgia), **neurologic** (peripheral neuropathy), **renal** (proteinuria, hematuria, MPGN, RPGN), **pulmonary** (small airway disease), **rheumatologic** (Sjogren's, Raynaud's), splenomegaly, lymphadenopathy

DIAGNOSIS—**laboratory** (↑ cryoglobulin level >800 μg/L or cryocrit >1% over 3–6 months, hypocomplementemia, ↑ ESR/CRP), **clinical** (vasculitis, thrombosis), **pathological** (biopsy of affected organ), **secondary causes** (serum protein electrophoresis, ANA, RF, HCV, HBV, HIV serology)

PROGNOSIS—10-year survival 50%. Death usually due to infection or cardiovascular disease. At risk for end-stage renal disease, secondary non-Hodgkin lymphoma

TREATMENTS—treat underlying cause. For severe disease, consider steroids, plasmapheresis (for hyperviscosity syndrome, life-threatening vasculitis, RPGN requiring dialysis), and immunosuppressive therapy (cyclophosphamide)

Lancet 2012 379:9813

PORPHYRIA

INHERITANCE—mainly autosomal dominant with incomplete penetrance

PATHOPHYSIOLOGY—enzymatic defect in the heme synthesis pathway → continued production of toxic heme precursors by liver and RBC → accumulation in neurovisceral organs (acute porphyrias) and/or skin (cutaneous porphyrias), with specific symptoms related to the nature of precursors. There are seven types of porphyria representing defects at each of the seven steps of the pathway

CLINICAL FEATURES OF ACUTE PORPHYRIAS—acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria. Preceded by anxiety, restlessness, and insomnia → **autonomic**

PORPHYRIA (CONT'D)

neuropathy (tachycardia, hypertension, arrhythmia, abdominal pain, vomiting, constipation/diarrhea), **sensory neuropathy** (extremity pain, back pain, numbness), **motor neuropathy** (weakness), **cranial neuropathy** (dysarthria, dysphagia, dysphonia, facial paresis), **metabolic changes** (dark/red urine, hepatic dysfunction, hyponatremia), and sometimes **CNS symptoms** (confusion, hallucinations, seizures) → usually decline within a week. Occasionally may progress to diffuse muscle weakness with respiratory muscle paralysis

CLINICAL FEATURES OF CUTANEOUS PORPHYRIAS—variegate porphyria, hereditary coproporphyria, and porphyria cutanea tarda. Chronic photosensitive skin symptoms include excessive fragility, blistering and scarring, particularly on the back of hands, hypertrichosis, and hyperpigmentation of face

DIAGNOSIS—24 h urinary porphobilinogen, urinary ALA, urinary porphyrins, fecal porphyrins. Ideally collect samples during acute attack. Other tests include erythrocyte porphyrins, plasma fluorescence spectrum, enzyme activity, DNA analysis, and skin biopsy

TREATMENTS—for acute porphyria, **avoid precipitating** medications (http://porphyriafoundation.com/drug-database), alcohol and infections if possible, with mostly supportive treatments during an episode. High-dose carbohydrate (400 g/day) diet is recommended acutely and exogenous heme infusions (*hematin* 4 mg/kg IV q12h) should be considered. For cutaneous porphyria, **avoidance of sun** is the only preventative strategy

Lancet 2005 365:241

WHIPPLE'S DISEASE

PATHOPHYSIOLOGY—*Tropheryma whipplei* (Gram positive bacillus, non-acid-fast, periodic acid-schiff positive) → infiltration of various organs without significant inflammatory response → accumulation of organisms eventually causing organ failure. White male predominance, mean age 50

CLINICAL FEATURES—**GI** (diarrhea, abdominal pain, malabsorption with weight loss and iron deficiency, GI bleed, abdominal mass), **joints** (polyarthritis, polyarthralgia. Joint symptoms may precede others for years), **CNS** (delirium, dementia, seizures, coma, hypothalamic pituitary axis dysfunction, cerebellar ataxia, meningitis, myelopathy), **eyes** (supranuclear vertical gaze palsy, oculomasticatory myorhythmia, and oculofacial–skeletal myorhythmia are pathognomonic), **skin** (hyperpigmentation, subcutaneous nodules, purpura), **cardiac** (myocarditis, pericarditis, culture negative endocarditis), pulmonary (interstitial fibrosis, pleural effusion, hilar lymphadenopathy), **hematologic** (anemia, lymphadenopathy), **constitutional** (fever, weight loss)

DIAGNOSIS—small bowel or tissue biopsy (PAS-positive macrophages). RT-PCR

TREATMENTS—antibiotics (*ceftriaxone* 2 g IV daily × 2 weeks, then *trimethoprim–sulfamethoxazole* DS 1 tab PO BID × 1–2 years), nutritional supplement (protein, iron, folate)

NEJM 2007 356:1

Related Topics
Chronic Liver Disease (p. 149)
Glomerulonephritis (p. 80)
Hepatitis C (p. 147)
Monoclonal gammopathy (p. 199)

Perioperative Assessment for Non-cardiopulmonary Surgery and Postoperative Complications

ACC Guidelines 2014

PERIOPERATIVE CARDIAC RISK ASSESSMENT

ACC/AHA PERIOPERATIVE SUMMARY

- **DEFINING SURGICAL URGENCY**
  - **EMERGENCY PROCEDURE**—limb/life-threatening and operation to be performed within <6 h
  - **URGENT PROCEDURE**—limb/life-threatening and operation within 24 h
  - **TIME SENSITIVE PROCEDURE**—a delay of >1–6 weeks for evaluation may negatively affect outcome (e.g. oncologic procedures)
  - **ELECTIVE**—procedure can be delayed for up to 1 year

PERIOPERATIVE CARDIAC RISK ASSESSMENT (CONT'D)

- **ACTIVE CARDIAC CONDITIONS**
  - **UNSTABLE CORONARY SYNDROMES**—unstable or severe angina* (CCS class III or IV), recent MI decompensated heart failure (NYHA functional class IV; worsening or new-onset heart failure)
  - **SIGNIFICANT ARRHYTHMIAS**—high-grade AV block, Mobitz II AV block, 3rd degree AV block, symptomatic ventricular arrhythmias, supraventricular arrhythmias (including

PERIOPERATIVE CARDIAC RISK ASSESSMENT (CONT'D)

atrial fibrillation) with uncontrolled ventricular rate >100 bpm at rest, symptomatic bradycardia, newly recognized ventricular tachycardia
  - **SEVERE VALVULAR DISEASE**—severe aortic stenosis (mean pressure gradient >40 mmHg, aortic valve area <1.0 cm^2, or symptomatic), symptomatic mitral stenosis (progressive dyspnea on exertion, exertional presyncope, or heart failure)
- **PROCEDURE RISK**
  - **VASCULAR** (cardiac risk >5%)—aortic and other major vascular surgery, peripheral vascular surgery
  - **INTERMEDIATE** (cardiac risk 1–5%)—intraperitoneal and intrathoracic surgery, carotid endarterectomy, head and neck surgery, orthopedic surgery, prostate surgery
  - **LOW** (cardiac risk <1%)—endoscopic procedures, superficial procedure, cataract surgery, breast surgery, ambulatory surgery
- **METABOLIC EQUIVALENT**
  - **1 MET**—ADLs (eat, dress, use toilet)
  - **2–3 MET**—walk indoors, walk one to two blocks on level ground at 3.2–4.8 km/h [2–3 mi/h]
  - **4 METS**—climb 1 flight of stairs, light housework such as dusting or washing dishes
  - **5–9 METS**—recreational activities, walk on level ground at 6.4 km/h [4 mi/h], run a short distance, heavy housework such as scrubbing floors or lifting heavy furniture
  - **10 METS**—strenuous sports such as swimming, tennis, football, basketball, skiing
- **OVERALL ALGORITHM**
  1. **Need for emergency non-cardiac surgery?** Yes = proceed to surgery with perioperative monitoring and postoperative risk factor management; no = proceed to step 2
  2. **Does the patient have an ACS?** Yes = refer for cardiology evaluation, manage for UA/NSTEMI/STEMI per guidelines; no = proceed to step 3
  3. **Estimate perioperative risk of major adverse cardiac event (MACE)** based on combined clinical/surgical risk. Low risk (<1%) = proceed to surgery without further testing; elevated risk >1% = proceed to step 4
  4. **Functional capacity greater than or equal to four METs without symptoms?** Yes = proceed with planned surgery; no or unknown = proceed to step 5

PERIOPERATIVE CARDIAC RISK ASSESSMENT (CONT'D)

  5. **Will further testing impact decision-making or perioperative care?** Yes = pharmacologic stress testing with dobutamine stress echocardiogram or pharmacological stress myocardial perfusion imaging (if abnormal, coronary revascularization according to guidelines); no = proceed to surgery OR consider alternative non-invasive treatment strategies/palliation
- **ALGORITHM FOR PATIENTS WHO REQUIRE PERCUTANEOUS CORONARY INTERVENTION PRIOR TO SUBSEQUENT SURGERY**
  1. For patients with acute MI, high-risk ACS or high-risk cardiac anatomy, **what is the bleeding risk of surgery?** Low = stent and continue dual-antiplatelet therapy; not low = proceed to step 2
  2. **What is the timing of planned surgery?** 14–29 days = perform balloon angioplasty; 30–365 days = use bare metal stent; >365 days = use drug eluting stent
- **ALGORITHM FOR PATIENTS WITH PREVIOUS PERCUTANEOUS CORONARY INTERVENTION**
  1. **Was the coronary stent implanted <4 weeks ago?** Yes = proceed to step 2; no = proceed to step 3
  2. **Is the patient scheduled for elective surgery after recent coronary stent?** Yes = delay surgery until after optimal period (30 days for bare metal stent, 1 year for drug-eluting stent); no = continue dual antiplatelet therapy (DAPT) peri-operatively unless risk of bleeding greater than risk of stent thrombosis
  3. **Did the patient have a drug-eluting stent implanted >30 days but <365 days ago?** Yes = proceed to step 4; no = proceed to step 5
  4. **Is the risk of surgical delay greater than risk of drug-eluting stent thrombosis?** Yes = proceed to surgery after 180 days; no = delay surgery until after optimal period of DAPT (30 days for bare metal stent, 1 year for drug eluting stent)
  5. **Does the surgery demand discontinuation of P2Y12 inhibitors?** Yes = continue ASA, restart $P2Y_{12}$ as soon as possible after surgery; no = continue current DAPT regimen
  6. **Did the patient have Balloon angioplasty without stenting?** If >14 days between angioplasty and planned surgery, proceed to surgery with ASA

PERIOPERATIVE CARDIAC RISK ASSESSMENT (CONT'D)

LEE CRITERIA (REVISED CARDIAC RISK INDEX)

- **HIGH-RISK SURGERY**—thoracic, intraperitoneal, or suprainguinal vascular surgery
- **CAD**—any MI, current angina, current nitrate use, positive exercise stress test, Q in ECG
- **HF**—history of HF, PND, pulmonary edema, S3, crackles, vascular redistribution on CXR
- **CVD**—history of stroke or TIA
- **DIABETES**—using insulin
- **RENAL FAILURE**—creatinine >175 μmol/L [1.9 mg/dL]
- **RISK OF MAJOR CARDIAC COMPLICATIONS**—**0/6** = 0.5% (0.4–0.5%), **1/6** = 1% (0.9–1.3%), **2/6** = 5% (4–7%), ≥**3/6** = 10% (9–11%)

PERIOPERATIVE PULMONARY RISKS

PATIENT—age >70, COPD, asthma, smoking (>40 pack year), poor general health status (ASA >2, see below), albumin <35 g/L [<3.5 g/dL], positive cough test. Note obesity is not a risk factor

PROCEDURE—nasogastric tube insertion perioperatively, upper abdominal, thoracic, and abdominal aortic aneurysm surgery, surgery >3 h, intraoperative pancuronium, general anesthesia

AMERICAN SOCIETY OF ANESTHESIOLOGISTS (ASA) CLASSIFICATION

- **1**—healthy patient with no disease outside of surgical process (<0.03% mortality)
- **2**—mild to moderate systemic disease caused by the surgical condition or other diseases, medically well controlled (0.2% mortality)
- **3**—severe disease process which limits activity but is not incapacitating (1.2% mortality)
- **4**—severe incapacitating disease process that is a constant threat to life (8% mortality)
- **5**—moribund patient not expected to survive 24 h with or without an operation (34% mortality)
- **E**—suffix for emergency surgery for any class

INVESTIGATIONS FOR PERIOPERATIVE PATIENTS

BASIC—CBCD, lytes, urea, Cr, INR, PTT, X-match

CARDIAC

- **ECG**—should be obtained in most patients, especially if CAD or structural heart disease or age >50
- **NON-INVASIVE TESTING** (exercise stress test, stress MIBI, dobutamine stress echocardiogram)—consider if high or intermediate clinical predictors, high-risk surgical procedures, and/or poor/unknown functional capacity (<4 METs). Assessment of left ventricular function indicated if dyspnea of unknown origin, HF with worsening dyspnea or change in clinical status. See ACC/AHA summary for more details
- **ANGIOGRAPHY**—not routinely indicated. Consider if high risk based on non-invasive testing, equivocal non-invasive test results in patients at high clinical risk undergoing high-risk surgery, angina unresponsive to medical treatment, unstable angina, especially if intermediate/high-risk surgery

PULMONARY

- **ABG**—for patients undergoing CABG, upper abdominal surgery, or lung resection with underlying lung disease or unexplained dyspnea. Provides baseline but not useful for risk stratification. Chronic hypercapnea might lead to the need for post- operative ventilatory support
- **CXR**—should be obtained if age >60 or suspect/known lung pathologies
- **PULMONARY FUNCTION TESTS**—patients undergoing thoracic or upper abdominal surgery with unexplained dyspnea and for those with COPD or asthma where clinical evaluation cannot determine if airflow obstruction has been optimally reduced
- **LUNG RESECTION WORKUP**—patients with preoperative FEV1 > 2 L (>80% predicted) and DLCO >80% predicted can probably tolerate pneumonectomy. Patients with FEV1 < 2 L or DLCO <80% predicted should have predicted postoperative FEV1 and DLCO calculated by perfusion scan or anatomic method. Patients with predicted postoperative FEV1 and DLCO >60% predicted can probably tolerate lung resection. Predicted postoperative FEV1 or DLCO <40% suggests high postoperative risk. Formal cardiopulmonary exercise testing (CPET) recommended if unclear risk or predicted postoperative FEV1 or DLCO <30%; patients with VO_2max >20 mL/kg/min will likely tolerate surgery

NEJM 1999 340:12
CHEST 2013 143:e166S-90S

MANAGEMENT OF PERIOPERATIVE PATIENTS

1. **REASON FOR CONSULT**—determine the reason for surgery and try to answer specific questions from the referring physician. Next, explore the 8 key domains of perioperative assessment

MANAGEMENT OF PERIOPERATIVE PATIENTS (CONT'D)

2. **CARDIAC RISK OPTIMIZATION**
   - **OPTIMAL TIMING**—**myocardial infarction** (wait 4–6 weeks if small to moderate MI. Wait >3 months if severe MI or LV dysfunction). **Angioplasty** (see ACC/AHA algorithm for patients with previous PCI). **CABG** (wait at least 1 month)
   - **OVERALL ELIGIBILITY**—if no acute MI, acute HF, severe mitral or aortic stenosis, severe arrhythmia will likely be able to go for surgery
   - **PREOPERATIVE**—**β-blockers** (continue β-blockers in patients already on therapy; do not initiate β-blocker therapy within 24 h of surgery due to increased risk of stroke, hypotension, bradycardia, death; for patients with intermediate/high risk MI in preoperative risk stratification or RCRI ≥3, consider early post-op initiation of β-blockade). **CABG** (indications include disabling angina despite maximal medical therapy, >50% stenosis of left main coronary artery, >70% stenosis of proximal LAD and proximal circumflex, 3-vessel disease with involvement of proximal LAD and poor LV function, 1- or 2-vessel disease with large area of viable myocardium, ongoing ischemia in NSTEMI unresponsive to medical therapy, STEMI after PCI-failure). **Angioplasty** (see ACC/AHA algorithm for patients who require PCI prior to subsequent surgery; indicated if STEMI/NSTEMI, left main disease but comorbidities precluding CABG). **Valvular surgery** (e.g. symptomatic aortic stenosis. If indicated should be done before elective non-cardiac surgery. If urgent surgery and severe aortic or mitral stenosis, consider balloon valvuloplasty)
   - **POSTOPERATIVE**—daily ECG and troponin × 3 days if high-risk and patient unable to communicate angina

AHA Guidelines 2014

3. **BACTERIAL ENDOCARDITIS PROPHYLAXIS**—only given to patients with the highest risk of developing endocarditis, which include the following
   - **HIGH-RISK CARDIAC CONDITIONS**
     - **PROSTHETIC**—any prosthetic cardiac valve, prosthetic material used for cardiac valve repair
     - **CYANOTIC CONGENITAL HEART DISEASE**—unrepaired, recently repaired (<6 months), completely repaired but with residual defects at the site or adjacent to the site of the prosthetic device
     - **CARDIAC TRANSPLANT RECIPIENTS WITH REGURGITANT VALVULOPATHY**
     - **PREVIOUS ENDOCARDITIS**
   - **PROCEDURES**
     - **ORAL CAVITY**—manipulation of gingival or periapical region of teeth, perforation of oral mucosa
     - **RESPIRATORY TRACT**—if incision/biopsy of respiratory mucosa (tonsillectomy, adenoidectomy), bronchoscopy with a rigid bronchoscope, or flexible bronchoscopy if biopsy performed
     - **GI/GU TRACT**—generally not recommended in the absence of active infection
     - **MSK**—if infected skin, skin structure, or musculoskeletal tissue
   - **PROPHYLAXIS REGIMENS**—give one of the following 30–60 min prior to procedure: *amoxicillin* 2 g PO/IM/IV, *cefazolin* 1 g IV/IM, *ceftriaxone* 1 g IV/IM, *cephalexin* 2 g PO, *clindamycin* 600 mg PO/IM/IV, *azithromycin* 500 mg PO, *clarithromycin* 500 mg PO

AHA Guidelines 2007

4. **PULMONARY RISK OPTIMIZATION**
   - **PREOPERATIVE**—smoking cessation for >8 weeks. Manage obstructive lung diseases (*ipratropium* 0.25 mg INH QID for all COPD patients, *salbutamol* 2.5 mg INH q4h PRN for all COPD/asthma patients with wheezing, and steroids if exacerbations). Antibiotics and delay surgery if lower respiratory infection is present. Patient education regarding lung expansion maneuvers
   - **INTRA-OPERATIVE**—**limit duration** of surgery to <3 h. **Avoid general anesthetics** (use spinal or epidural anesthesia, regional anesthesia). **Avoid pancuronium. Laparoscopic procedures** when possible. **Substitute** less ambitious procedure for upper abdominal or thoracic surgery when possible
   - **POSTOPERATIVE**—**deep-breathing exercises** or **incentive spirometry. CPAP** if needed. **Pain control** (consider epidural analgesia or intercostal nerve blocks)
5. **MEDICATION MANAGEMENT**
   - **CARDIOVASCULAR AGENTS**—**β-blockers** (continue up to and including day of surgery. If prolonged NPO, substitute with

MANAGEMENT OF PERIOPERATIVE PATIENTS (CONT'D)

IV labetalol, propanolol, or metoprolol). **α-Agonists** (continue up to and including day of surgery. If prolonged NPO, substitute with TD clonidine or IV methyldopa). **Calcium channel blockers** (continue up to and including day of surgery. If prolonged NPO, no IV substitute unless poor hemodynamics). **ACE inhibitor/ARB** (continue up to and including day of surgery if for hypertension, but consider holding day of surgery if for HF. If prolonged NPO, use IV β-blocker if hypertension and hydralazine/nitrate if HF). **Diuretics** (continue up to day before surgery but stop day of surgery. If prolonged NPO, use IV form on PRN basis). **Statins** (continue up to and including day of surgery). **Fibrates/niacin/cholestyramine/ezetimibe** (continue up to day before surgery but stop day of surgery)

- **ANTIPLATELET AGENTS**—**ASA** (usually not stopped unless high-risk of bleed, e.g. CNS surgery. If so, hold 7–10 days before surgery and restart 6 h postop). See AHA Guidelines for anti-platelet management post-MI or coronary stent. **Dipyridamole** (similar to ASA in terms of indications for stopping. If stop, hold at least 2 days before surgery). **Aggrenox** (discontinue 7–10 days before surgery). **Clopidogrel and ticagrelor** (dependent on indication: often standard to hold 7–10 days before surgery. If used following angioplasty, continue for at least 6 weeks before stopping. Continue combination clopidogrel + ASA for at least 1 month for bare-metal stents and 12 months for drug-eluting stents. Premature discontinuation of dual antiplatelet therapy increases risk of perioperative cardiac death 5–10×, incidence 30%. Combination clopidogrel + ASA increases absolute risk of major perioperative bleeding by 0.4–1% compared to ASA alone. Generally, most surgeries can be performed without discontinuing antiplatelet therapy for recent coronary stenting, except neurosurgery or posterior chamber eye surgery). **NSAIDs** (some vascular protective effect but also potential renal failure. Hold 3 days before surgery, substitute with acetaminophen as needed)

MANAGEMENT OF PERIOPERATIVE PATIENTS (CONT'D)

- **ANTICOAGULATION**—decision to interrupt anticoagulation depends on risk of thrombosis and estimation of procedural bleeding risk (type of surgery, urgency). If emergent surgery, administer IV vitamin K, FFP/prothrombin complex concentrate as required. Elective surgery should be delayed at least 1 month after treatment of venous or arterial thromboembolism. **Warfarin** (if low perioperative bleeding risk, no need to disrupt warfarin; if high perioperative bleeding risk, keep INR <1.5 by stopping warfarin 5 days preoperatively and resume 12–24 h after surgery and hemostasis achieved). **Novel oral anticoagulants** (dabigatran and rivaroxaban should be discontinued 2–4 days before surgery depending on renal function, bleeding risk of surgery; apixaban discontinued 2–3 days before surgery). **Bridging anticoagulation** (generally not required for novel oral anticoagulants unless very high risk of thrombosis, prolonged period of discontinuation; for vitamin K antagonists, bridging with therapeutic dose LMWH or IV unfractionated heparin if high risk of thromboembolism vs. no bridging required if low risk of thromboembolism. If moderate risk of thromboembolism, decide based on individual patient-related and surgery-related factors. Stop bridging LMWH 24 h prior to operation, stop UFH 4–6 h prior to operation)

CHEST Guidelines 2013

- **STEROIDS**—patients taking prednisone >20 mg/day for >3 weeks or with Cushingoid features should be assumed to have HPA axis suppression. For **minor stress** (local anaesthetic), no stress dose steroids needed. For **moderate stress** (orthopedic, perivascular), consider 2× physiologic replacement (*hydrocortisone* 50 mg IV on call to OR, then 25 mg q8h × 24 h, then normal dose). For **major stress** (intra-abdominal, cardiac), consider high-dose steroid (*hydrocortisone* 100 mg IV on call to OR, then 50 mg q8h × 24 h, then 25 mg q8h × 24 h, then resume maintenance)

MANAGEMENT OF PERIOPERATIVE PATIENTS (CONT'D)

Risk Category	Mechanical Heart Valve	Atrial Fibrillation	Venous Thromboembolism
High	Any MV prosthesis, caged ball/tilting disc AV, recent CVA/TIA <6 months	$CHADS_2$ 5 or 6, rheumatic valvular heart disease, recent CVA/TIA <3 months	Recent VTE <3 months, severe thrombophilia (protein C/S deficiency, AT-III, APA, multiple abnormalities)
Moderate	Bileaflet AV and ≥1 of AF, CVA/TIA, HTN, DM, HF, age >75	$CHADS_2$ 3–4	VTE within 3–12 months, non-severe thrombophilia (heterozygous factor V Leiden, prothrombin gene mutation), recent VTE, active cancer (<6 months or palliative)
Low	Bileaflet AV prosthesis without atrial fibrillation or other risk factors for stroke	$CHADS_2$ 0–2	VTE >12 months previous and no other risk factors

MANAGEMENT OF PERIOPERATIVE PATIENTS (CONT'D)

- **DIABETIC AGENTS**—key principle is to avoid hypoglycemia and hyperglycemia. **Oral hypoglycemics** (continue up to day before surgery and discontinue AM dose on day of surgery. If prolonged NPO or hyperglycemia, substitute with insulin sliding scale). **Insulin** (decrease nighttime insulin dose by half the night prior to surgery and omit morning insulin the day of surgery. For short procedures, may give 1/3 to 1/2 long-or intermediate-acting insulin dose. For complicated procedures, type 1 diabetics, or volatile sugar levels in type 2 diabetics, consider insulin drip)
- **THYROID AGENTS**—**levothyroxine** (T4) may be given IV (80% of PO dose) if oral intake cannot be resumed for a prolonged period of time. Otherwise, can miss a few days without clinical impact (half-life 7 days)
- **NEUROLOGIC AGENTS**—**anti-epileptics** (continue up to and including day of surgery. If NPO, substitute with IV phenytoin or phenobarbital). **Antidepressants/Li** (continue up to day before surgery but stop day of surgery. Resume postop with oral intake)

6. **DVT PROPHYLAXIS**—early ambulation, intermittent pneumatic compression, low-dose heparin, LMWH, coumadin
7. **BLEEDING RISK ASSESSMENT**—inquire about any recurrent bleeding tendencies and bleeding complications from past surgeries. Review Hb, platelets, INR, and PTT
8. **ANESTHETIC RISK ASSESSMENT**—inquire about past surgeries and family history of malignant hyperthermia
9. **DELIRIUM RISK ASSESSMENT**—inquire about alcohol and illicit drug use, diagnosis of dementia to assess the risk of post-operative delirium

MANAGEMENT OF PERIOPERATIVE PATIENTS (CONT'D)

POSTOPERATIVE COMPLICATIONS

MAJOR CARDIAC COMPLICATIONS—myocardial infarction, arrhythmia

MAJOR PULMONARY COMPLICATIONS—pneumonia, respiratory failure with prolonged mechanical ventilation, bronchospasm, atelectasis, exacerbation of underlying chronic lung disease

HEMATOLOGIC COMPLICATIONS—bleeding, thrombosis

POSTOPERATIVE FEVER ★7WS★

- **W**ound—infection
- **W**ind—pulmonary (pneumonia, atelectasis, PE)
- **W**eins ('veins')—DVT/PE
- **W**ater—UTI
- **W**onder drugs
- **W**hat the heck—sepsis
- **W**hat else—thyroid storm

POSTOPERATIVE COMPLICATIONS (CONT'D)

POSTOPERATIVE DELIRIUM ★DIMS★

(see p. 432 for more details)

- **D**rugs—alcohol withdrawal, benzodiazepines, pain (i.e. lack of appropriate drugs)
- **I**nfections—pneumonia, UTI, sepsis
- **M**etabolic—myocardial infarction, hypoxia (pulmonary embolism), electrolyte abnormalities
- **S**tructural—stroke, intracranial hemorrhage

POSTOPERATIVE HYPERTENSION

(see p. 65 for more details)

- **PHYSIOLOGIC**—pain, bladder distension/atony, confusion/agitation, thyroid storm
- **PATHOLOGIC**—infections, stroke
- **DRUGS**—alcohol withdrawal, withdrawal of antihypertensive medications, neuroleptic malignant syndrome, malignant hyperthermia

POSTOPERATIVE ACUTE RENAL FAILURE

(see p. 78 for more details)

- **PRE-RENAL**—blood loss, fluid loss, ACE inhibitors, NSAIDs, cyclosporin
- **RENAL**—ATN (ischemic, contrast, aminoglycosides), AIN (penicillins, cephalosporins), microvascular (cholesterol emboli)
- **POST-RENAL**—urinary retention

POSTOPERATIVE COMPLICATIONS (CONT'D)

POSTOPERATIVE BLEEDING

(see p. 170 for more details)

- ↑ **INR**—factor deficiency or inhibitor (VII), liver disease, vitamin K deficiency, DIC, warfarin
- ↑ **INR AND PTT**—factor deficiency (X, V, II, I), liver disease, vitamin K deficiency, DIC, warfarin
- ↑ **PTT**—factor deficiency and inhibitor (VIII, IX, XI), heparin, von Willebrand disease
- **PLATELET DISORDER**—von Willebrand disease, renal failure, liver failure, myeloproliferative disorders

POSTOPERATIVE THROMBOCYTOPENIA

(see p. 167 for more details)

- **PSEUDOTHROMBOCYTOPENIA**—platelet clumping (recollect in citrate)
- **DILUTIONAL**—transfusions, bleeding
- **DECREASED PRODUCTION**—less likely but possible
- **SEQUESTRATION**—less likely but possible
- **DESTRUCTION**—DIC, drugs (HITT with heparin, GPIIb/IIIa inhibitors, thiazides, sulfonamides, rifampin, indomethacin), alloimmune (post-transfusion)

Medical Fitness to Drive

GENERAL PRINCIPLES

DRIVER'S LICENSING AUTHORITY—responsible for issuing/revoking licenses

PHYSICIANS—responsible for reporting unfit drivers. In some jurisdictions, it is mandatory to report. The physicians can be held liable for negligence if a patient is involved in a motor vehicle accident

UNCERTAINTY—if not sure about medical fitness for driving, advise patient not to drive. Document it and inform the Ministry of Transportation

GENERAL PRINCIPLES (CONT'D)

BALANCE—interest of public has priority over rights of individual driver

LICENSE TYPE—professional license vs. private vehicle

OLDER DRIVERS—★CANDRIVE★ (**C**ognition, **A**cute or fluctuating illness, **N**euromuscular disease or neurological effects, **D**rugs, **R**ecord prior accidents, **I**n-care experiences suggesting high-risk, **V**ision, **E**thanol use)

DURATION OF NO DRIVING FOR SPECIFIC DISORDERS

GENERAL PRINCIPLES (CONT'D)

Disorders	Private driver	Professional driver
Seizures		
Single, unprovoked seizure before diagnosis	3 months, neuro assessment needed (with EEG, imaging)	12 months
Epilepsy	6 months (seizure-free on meds)	5 years (seizure-free on or off meds)
Seizures after initiating or changing anti-epileptics	3 months	6 months
Alcohol withdrawal seizures	6 months (alcohol and seizure free, adherent and completed rehabilitation)	6 months (alcohol and seizure free, adherent and completed rehabilitation)
Syncope		
Vasovagal syncope ×1	No restriction	No restriction
Unexplained syncope ×1 or recurrent vasovagal syncope	1 week	12 months
Recurrent unexplained syncope	3 months	12 months
Cardiovascular		
Stable angina	No restrictions	No restrictions
Unstable angina	48 h after PCI, 7 days after discharge if no PCI	7 days after PCI, 30 days after discharge if no PCI
STEMI or non-STEMI	1 month after discharge	3 months after discharge
PCI	48 h	7 days
CABG	1 month	3 months
Heart failure	No if NYHA IV, home inotropes, or LV assist	No if NYHA ≥ III, EF <35%
Unstable or sustained VT with LVEF <35%, VF	3–6 months after event	No driving
SVT, AF or Atrial flutter	No restriction if no impairment in consciousness, satisfactory rate control; consider anticoagulation	No restriction if no impairment in consciousness, satisfactory rate control; consider anticoagulation
Mobitz II 2° AVB, acquired 3° AVB, alternate LBBB or RBBB	No driving	No driving
Permanent Pacemaker	1 week after implant (regular PM checks required)	
ICD	4 weeks to 6 months	Disqualified
AAA	No if >6 cm (men), >5.5 cm (women)	
Cerebrovascular		
TIA	If no symptoms	If no symptoms
Stroke	1 month	1 month
Other disorders		
Vision	No if poor vision <20/50, hemianopsia, or diplopia	No if poor vision <20/30, hemianopsia, or diplopia
Diabetes on insulin	Must have no microvascular or macrovascular complications that impair capacity to drive and no episodes of severe hypoglycemia in last 6 months while awake	Must have regular physician monitoring and cannot have uncontrolled DM (including A1c over 12%). See Canadian Diabetes Guidelines for details. Must have no microvascular or macrovascular complications that impair capacity to drive and no episodes of severe hypoglycemia in last 6 months while awake
COPD	No if on home O_2 (need road test, annual reassessment)	No if on home O_2

NOTE: regulations for reporting/restriction in individual jurisdictions may vary

CMA Driver's Guide 8th Ed

Obtaining Consent for Medical Procedures

CONSENTING PROCESS

CONTEXT—establish an appropriate setting for the discussion

WHAT DOES THE PATIENT UNDERSTAND?

- "What do you understand about your illness?"
- "Have you had any similar procedures before?"
- Obtain a general impression of patient's competence

DISCUSS THE RATIONALE AND POTENTIAL BENEFITS REGARDING THE PROCEDURE, EXPLAIN DETAILS OF PROCEDURE

- **POSITIONING**
- **LOCAL ANESTHETIC**—ask about allergies
- **ACTUAL PROCEDURE**—degree of detail tailored to patient's comprehension and interest. Assess bleeding risk

CONSENTING PROCESS (CONT'D)

- **ESTIMATED DURATION**
- **POTENTIAL COMPLICATIONS**—bleeding, infections, puncture/injury of surrounding tissue, and other specific risks related to procedure

EXPLAIN ALTERNATIVES

(including risk of deferring procedure, step by step)

ASSESS UNDERSTANDING—use simple language and ask the patient to summarize what they understand

DISCUSS CONSENT FORM—patient may wish to read the consent form carefully and have some time to think about procedure

PROVIDE REASSURANCE AND FOLLOW-UP

Biomedical Ethics Issues

ETHICS JUDGMENT

MORAL JUDGMENT—the decision-making process is based on both ethics principles and facts

- **ETHICS PRINCIPLES**—beneficence, non-maleficence, autonomy, and justice
- **FACTS**—patient preference, competence, prognosis, and others (finances, resources)

TRUTH TELLING

EXAMPLE—patient's family members do not want bad news disclosed to patient

FACTORS TO CONSIDER—autonomy, loss of trust, patient will eventually find out, patient's need to make plans

APPROACH—ask patient if he/she wants bad news disclosed. Ensure good communication with family

EXCEPTIONS—specific cultures, harm to patient (legally may exercise therapeutic privilege, but seldom used)

INFORMED CONSENT

EXAMPLE—patient asks to stop treatment

FACTORS TO CONSIDER—autonomy, law, CMA policy

INFORMED CONSENT—disclosure (discuss condition, treatment proposed, alternatives, risks, and benefits), capacity (competence), and voluntariness

CAPACITY

EXAMPLE—patient refuses treatment but may not be competent

CAPACITY (CONT'D)

REQUIREMENT—ability to understand information and appreciate consequences of *individual* decision. Competence assessment may be required, involve multidisciplinary team (p. 427)

SUBSTITUTE DECISION MAKING—legally through advance directive proxy (also known as representative agreement or personal directive), the court, or court-appointed guardian (spouse > children > parents > siblings > relatives > public trustee). The selection of guardian is based on patient's wishes, values and beliefs more than his/her best interest judgment. Practically, however, decisions are usually made by family members and healthcare team together

BATTERY AND NEGLIGENCE

CRITERIA FOR BATTERY—doing anything (e.g. touching) without patient's consent

CRITERIA FOR NEGLIGENCE

1. Physician owes patient duty of care
2. Physician breaches standard of care
3. Breach causes harm to patient
4. Physician's mistake is responsible for patient's loss (causation)

CONFIDENTIALITY

EXAMPLE—HIV disclosure to spouse

FACTORS TO CONSIDER—autonomy, need trust for therapeutic relationship

APPROACH—breaching confidentiality is based on a balance of beneficence, non-maleficence,

CONFIDENTIALITY (CONT'D)

and autonomy. Legally can breach confidentiality if required by court/law, patient consent obtained, or if public interest at stake (e.g. HIV, child abuse, and people who are unfit to drive)

FUTILITY

EXAMPLE—CPR in patient with advanced cancer

FACTORS TO CONSIDER—limits of patient autonomy and considerations of justice and resource allocation

APPROACH—communication (understand patient's rationale), negotiation, mediation (bioethicist), and arbitration. No legal obligation to provide treatment outside of standard of care

MAY REFUSE PROVIDING TREATMENT—if harm to self/others, futility, or excessive cost to society

EUTHANASIA

EXAMPLE—ALS patient asks for active euthanasia

TYPES—active euthanasia is direct involvement of killing a patient (e.g. injection of KCl), while passive euthanasia is providing the means for the patient to kill himself (e.g. preparing KCl)

ARGUMENTS FOR—autonomy, the relief of suffering, and discrimination against physically disabled persons who cannot commit suicide

ARGUMENTS AGAINST—respect for human life, protection of vulnerable persons, and fear of abuse

LEGALLY—withdrawal of care and palliative sedation (for the purpose of maximizing comfort) are acceptable, but passive/active euthanasia not allowed based on intention and causation (varies by jurisdiction)

RESOURCE ALLOCATION

EXAMPLE—selection of organ transplant recipients

FACTORS TO CONSIDER—justice

1. No one disputes that resources are scarce and rationing decisions are required
2. It is unfair to ration based on implicit criteria that may vary from physician to physician

RESOURCE ALLOCATION (CONT'D)

3. Rationing criteria must be explicit, evenly applied, publicly known, and open to review
4. It is unfair to begin rationing by denying resources to the most vulnerable patients
5. An alternative to rationing is to augment the availability of the scarce resource

LEVELS—macro (provincial/national), meso (hospital), micro (individual patient)

RATIONING—discrimination on the basis of age, gender, or religion is legally and morally not feasible. Allocation based on greater benefit and/or more urgent need is acceptable. Financial considerations should be taken into account, but do not justify omission of appropriate care

RESEARCH ETHICS

EXAMPLE—placebo control

FACTORS TO CONSIDER—beneficence, nonmaleficence, autonomy, and justice. Physician torn between best interest of research community and patient

APPROACH—patient's right to care comes first

ETHICAL RESEARCH METHODS—clinical equipoise (there is genuine uncertainty within the expert medical community, not necessarily on the part of the individual investigator, about the preferred treatment between the various arms of a randomized controlled trial), good experimental design (treatment arms, likely benefit > harm, inclusion and exclusion criteria, respect rights of research subjects, informed consent), and ethics review board approval

CONFLICT OF INTEREST

EXAMPLE—pharmaceutical company funded pizza lunch

PROFESSIONAL JUDGMENT—physicians trusted by patients and society because of the fiduciary duty doctors accept to rank their primary interests (appropriate patient care, valid research, truthful, and unbiased teaching) above such secondary interests as personal gain, promotion, fame, or other benefits

APPROACH—cannot eliminate all conflicts of interest, as they are inextricable from our lives, but prevent secondary gain from dominating or appearing to dominate professional decisions or choices

Hospital Admission and Discharge Issues

PRINCIPLES OF MEDICAL MANAGEMENT

★THE 5CS★

CAUSES—identify and treat the underlying cause of disease

COMPLICATIONS—anticipate and treat complications as they arise

COMMUNICATION—educate patients regarding **lifestyle changes** and precautions (e.g. driving, sports, medical alert bracelet). Provide counseling on **risk reduction** (e.g. quit smoking, blood pressure, and lipid control) and **appropriate use of medications**

CONSULT—seek advice from other disciplines when indicated (physiotherapy, dietician, specialists)

CONTINUITY—provide appropriate follow-up

REASONS FOR ADMISSION

MEDICAL—diagnostic workup, monitoring, IV therapy (hydration, antibiotics, chemotherapy), surgery

NURSING—ADL assistance (eating, bathroom, mobility), monitoring (critically ill)

MENTAL—suicide or homicide risk due to psychiatric disorder

SOCIAL—usually in combination with factors above, cannot cope at home/lack of support, out-of-town, homeless

REHABILITATION CRITERIA

NOT DEMENTED
NOT DEPRESSED
MEDICALLY STABLE
POSSIBILITY FOR IMPROVEMENT
DISCHARGE PLAN AFTER REHABILITATION

DISCHARGE CRITERIA

CRITERIA—depends on the functional, medical, mental, and social situations

DISCHARGE PLANNING—should take place from the time of admission. The goal of hospital stay is to get the patient well enough to leave hospital

DISPOSITION

HOME ± COMMUNITY PROGRAMS—home care (clinical care, home IV, support services, coordinating care), day program (day hospital, day support)

SUPPORTIVE HOUSING—lodge/assisted living, group homes (mental, disabled)

CARE FACILITY—long-term care, respite, subacute, rehabilitation, psychiatry

PALLIATIVE CARE—palliative care unit, hospice

Appendix A

ADVANCED CARDIAC LIFE SUPPORT

2010 American Heart Association (AHA) Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science. **Circulation 2010 122:S729-S767**

Assess C-A-B
Activate Emergency Response
If pulseless, proceed to CPR right away
If pulse present, check pulse, BP, O2 sat
Give O2, monitor rhythm, IV access
Pulseless
Start CPR
Check rhythm
Tachycardia
If pulse present: identify/Rx underlying cause, maintain airway, oxygen, cardiac monitor, IV access, 12-lead ECG; do not delay therapy
Bradycardia
Asystole, PEA
VF/pulseless VT
CPR 2 min
Epinephrine
1 mg IV/IO q3–5min
Defibrillate x1
120–200 J (biphasic), or 360 J (monophasic)
CPR 2min
IV/IO, Airway
Rhythm Shockable?
No
Yes
CPR 2 min
Epinephrine
1 mg IV/IO q3–5 min
Treat reversible causes
12 lead ECG
NS 2 L IV
HCO3 2 amp
MgSO4 2 g IV
Chest decompression
Defibrillate x1
CPR 2 min
Epinephrine
1mg IV/IO q3–5 min
Airway Mx
Rhythm Shockable?
Defibrillate x1
CPR 2 min
Amiodarone
IV/IO
Rhythm Shockable?
If return of spontaneous circulation, post-cardiac arrest care
Unstable
Persistent tachycardia (typically HR>150) causing:
Hypotension
LOC change
Shock
Ischemic CP
Acute HF
Premedicate
Midazolam 1 mg IV q2–3min and/
Fentanyl 50–150 µg IV q5min
Ensure IV access, O2 sat monitor, intubation equipment, and suction available
Synchronized Cardioversion
Narrow regular: 50–100J
Narrow irregular: 120–200J (biphasic) or 200J (monophasic)
Wide regular: 100J
Wide irregular: defibrillation dose
Monitor ABC, prepare to intubate and give antiarrhythmics PRN
Stable
WIDE COMPLEX
VT
(most common)
SVT with BBB
AF with WPW
Antidromic AVRT
Monomorphic VT and no CHF:
Amiodarone
150 mg IV bolus over 10 min, followed by maintenance infusion or
Procainamide
20 mg/min (max 17 mg/kg)
Polymorphic VT with prolonged QT
MgSO4 2 g IV
Isoproterenol
0.02–0.04 mg IV push (if associated with bradycardia)
Overdrive pacing
Synchronized cardioversion — see ATRIAL FIBRILLATION
NARROW COMPLEX QRS <0.12 (IRREGULAR)
AF, Atrial flutter,
MAT
Diltiazem
15–20 mg (0.25mg/kg) IV over 2 min OR
Metoprolol
5 mg IV OR
Amiodarone
150 mg IV over 10 min OR
Digoxin
0.4–0.6 mg IV
— see ATRIAL FIBRILLATION for further details
Synchronized cardioversion — see ATRIAL FIBRILLATION
NARROW COMPLEX (REGULAR)
Atrial (sinus tachyHR, atrial flutter, ectopic),
Junctional,
PSVT (AVNRT, orthodromic AVRT-WPW)
Vagal maneuvers
(carotid massage, Valsalva)
Adenosine 6 mg rapid IV push. May repeat (12 mg)
If healthy heart
Verapamil
2.5–5mg IV OR
Diltiazem
15–20 mg IV
If LV failure
Diltiazem
15–20 mg IV OR
Digoxin
0.4–0.6 mg IV OR
Amiodarone
150 mg IV over 10 min
Synchronized cardioversion — see unstable tachycardia
Unstable
Hypotension
LOC change
Shock
Ischemic CP
Acute HF
Atropine 0.5 mg IV
Transcutaneous pacemaker OR
Dopamine
2–20 IV µg/kg/min OR
Epinephrine
2–10 µg/min IV
Transvenous pacemaker and expert consultation
Stable
1° AV block
Type I 2°
AV block
Monitor and observe
Type II 2°
AV block
3° AV block
Transcutaneous pacemaker
Transvenous pacemaker
Permanent pacemaker
Asystole/PEA DDx
Hypovolemia
Hypoxia
Hypothermia
Hyper/hypoK
H+ (acidosis)
Tablets/Toxins
Tamponade, cardiac
Tension pneumothorax
Thrombosis CAD/PE
Asystole/PEA drugs
Epinephrine 1 mg IV/IO push, q3–5min, or 2–2.5× IV dose via ETT in 10 mL of NS followed by hyperventilation if IV/IO not available
Vasopressin 40 U IV/IO push×1 dose (can replace 1st/2nd epi)
Atropine 1 mg IV push, q3–5min, max total 0.04 mg/kg (approximately 3 doses), 2–2.5×IV dose down endotracheal
VF/pulseless VT drugs
Epinephrine 1 mg IV/IO push, q3–5min
Vasopressin 40 U IV/IO push×1 dose (can replace 1st/2nd epi)
Amiodarone 1st dose 300 mg IV/IO push, 2nd dose 150 mg, max total 2.2 g/24 h
MgSO4 2 g IV if torsades de pointes or suspect hypoMg
HCO3 2 amp IV push if hyperkalemia, metabolic acidosis, TCA overdose, barbiturate overdose, ASA daily, etc. Avoid if respiratory acidosis
Biphasic Shock: 120-200 J (if unknown, use maximum available) vs. monophasic shock: 360 J
Tachycardia drugs
Amiodarone 150 mg IV bolus over 10 min, then 1 mg/min (60 mg/h) for 6 h, followed by 0.5 mg/min (30 mg/h) for 18 h. Maximum total 2.2 g/24 h
Procainamide 20–30 mg/min IV, maximum infusion at 17 mg/kg, maintenance at 1–4 mg/min. Indicated particularly for WPW with AF (wide complex irregular tachycardia). Administer until maximum dose reached, dysrrhytmia suppressed, QRS widens >50%, or hypotension occurs
Sotalol 100mg (1.5mg/kg) IV over 5 minutes. Avoid if prolonged QT.
Adenosine 6 mg rapid IV push, 2nd dose 12 mg, 3rd dose 12 mg. Indicated in PSVT. Avoid if WPW with AF
Amiodarone 150mg IV bolus over 10 min, q10–15min. Alternatively, infusion 360 mg over 6 h, then 540 mg over 18 h. Maximum total 2.2 g/24 h. Good for most SVT
β-Blocker: Metoprolol 5 mg IV q5min, may repeat ×2. Maximum total 15 mg,
Labetalol 10 mg IV q10min. Maximum total 150 mg
Calcium channel blocker: Diltiazem 0.25 mg/kg (10–20 mg) IV over 2 min, 2nd dose 0.35 mg/kg (25 mg), then infusion at 5–10 mg/h. Verapamil 2.5–5 mg IV over 2 min, repeat 15–30 min. Avoid if WPW with AF
Digoxin 0.4–0.6 mg IV, then 0.1–0.3 mg q6–8h. Then 0.125–0.5 mg IV/PO daily
Bradycardia drugs
Atropine 0.5 mg IV bolus, repeat q3–5min, max 3mg, 2–2.5 × IV dose down endotracheal tube in 10 mL NS if needed. Unlikely beneficial in third degree or Mobitz type II block
Dopamine 2–20 µg/kg/min IV, after max dose of atropine
Epinephrine 2–10 µg/min IV, if severe bradycardia with hypotension
Important Principles
C-A-B Approach – Chest compressions, Airway, Breathing – chest compressions should not be delayed and should be started even before rescue breathing.
CPR—ensure good compressions by allowing chest to recoil fully and minimizing interruptions. Aim for 100 compressions per minute for 2 min each cycle. Continue until regain pulse. The focus for initial resuscitation should be on performing high-quality CPR. Frequent pulse check, intubation, central line insertion, and medications may sometimes distract the team from this important task.
Airway—avoid hyperventilation as this could increase intrathoracic pressure. Initial use of oropharyngeal airway with bag -valve mask is reasonable, with 2 breaths given after every 30 CPR compressions. Once switched to advanced airway (laryngeal mask airway, co mbitube, or endotracheal tube), breaths should be given every 6 s
Access—the preferred route is through a peripheral intravenous (IV) line, which can usually be established easily. The intraosseous (IO) route represents a second choice, while central lines and endotracheal tube should be the last resort for medication access

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Appendix B
LIST OF COMMON ABBREVIATIONS

% sat	Percentage saturation
5-FU	5-Fluorouracil
5-HIAA	5-Hydroxyindoleacetic acid
5HT	Serotonin
AAA	Abdominal aortic aneurysm
ABC	Airway, breathing, circulation
Abd	Abdomen
ABG	Arterial blood gas
ABI	Ankle brachial index
ABPA	Allergic bronchopulmonary aspergillosis
ABx	Antibiotics
ACE	Angiotensin-converting enzyme
ACI	Acute cardiac ischemia
ACR	American College of Rheumatology
ACS	Acute coronary syndrome
ACTH	Adrenocorticotropic hormone
ADL	Activity of daily living
ADP	Adenosine diphosphate
AF	Atrial fibrillation
AFB	Acid fast bacilli
AFP	Alpha fetoprotein
AG	Anion gap
AIDS	Acquired immunodeficiency syndrome
AIN	Acute interstitial nephritis
AJR	Abdominal jugular reflex
AKI	Acute kidney injury
ALI	Acute lung injury
ALL	Acute lymphoblastic lymphoma
ALND	Axillary lymph node dissection
ALS	Amyotrophic lateral sclerosis
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AMA	Antimitochondrial antibody
AMI	Acute myocardial infarction
AML	Acute myelogenous leukemia
ANA	Antinuclear antibody
ANC	Absolute neutrophil count
ANCA	Anti-neutrophilic cytoplasmic antibody
AP	Anterior–posterior
APA	Antiphospholipid antibody
APACHE	Acute physiology and chronic health evaluation
APC	Adenomatosis polyposis coli
APS	Antiphospholipid antibody syndrome
ARB	Angiotensin receptor blocker
ARDS	Acute respiratory distress syndrome
ARR	Absolute risk reduction
AS	Aortic stenosis
ASA	Acetylsalicylic acid, American Society of Anesthesiologists
ASD	Atrial septal defect
ASO	Anti-Streptolysin-*O*
AST	Aspartate aminotransferase
ATC	Around the clock
ATN	Acute tubular necrosis
AV	Atrioventricular or arteriovenous
AVM	Arteriovenous malformation
AVNRT	Atrioventricular nodal reentry tachycardia
AXR	Abdominal X-ray
BAC	Bronchioloalveolar carcinoma
BAL	Bronchoalveolar lavage
BCC	Basal cell carcinoma
BID	Twice per day
Bili	Bilirubin
BIPAP	Bilevel positive airway pressure
BL	Burkitt's lymphoma
BMD	Bone mineral density
BMI	Body mass index
BMR	Basal metabolic rate
BMT	Bone marrow transplant
BNP	B-type natriuretic peptide
BOOP	Bronchiolitis obliterans organizing pneumonia
BP	Blood pressure
BPPV	Benign paroxysmal positional vertigo
BRBPR	Bright red blood per rectum
BRCA	Breast cancer gene
BSA	Body surface area
BSE	Breast self-examination
C&S	Culture and sensitivity
Ca	Calcium
CA 125	Cancer antigen 125
CA 15.3	Cancer antigen 15.3
CA 19–9	Cancer antigen 19–9
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CAH	Congenital adrenal hyperplasia
CAM	Confusion Assessment Method
CA-MRSA	Community-acquired methicillin-resistant *Staphylococcus aureus*
CAP	Community-acquired pneumonia
CAPD	Continuous ambulatory peritoneal dialysis
CBC	Complete blood count
CBCD	Complete blood count and differential
CBE	Clinical breast examination
Cbl	Cobalamin
CCB	Calcium channel blocker
CCP	Cyclic citrullinated peptides
CCS	Canadian Cardiovascular Society
CEA	Carcinoembryonic antigen

CHF	Congestive heart failure
Chol	Cholesterol
CIN	Cervical intraepithelial neoplasia
CK	Creatine kinase
CKD	Chronic kidney disease
CKMB	Creatine kinaseMB
Cl	Chloride
CLL	Chronic lymphocytic leukemia
CMA	Canadian Medical Association
CMC	Carpometacarpal joint
CML	Chronic myelogenous leukemia
CMML	Chronic myelomonocytic leukemia
CMV	Cytomegalovirus
CN	Cranial nerve, cyanide
CNS	Central nervous system
CO	Carbon monoxide, cardiac output
COP	Cryptogenic organizing pneumonia
COPD	Chronic obstructive pulmonary disease
COX	Cyclooxygenase
CPAP	Continuous positive airway pressure
CPR	Cardiopulmonary resuscitation
CR	Controlled release, complete remission
Cr	Creatinine
CrCl	Creatinine clearance
CRF	Chronic renal failure
CRH	Corticotropin-releasing hormone
CRP	C-reactive protein
CRT	Cardiac resynchronization therapy
CSF	Cerebrospinal fluid
CT	Computed tomography
CVA	Cerebral vascular disease, costovertebral angle
CVC	Central venous catheter
CVD	Cerebral vascular disease
CVP	Central venous pressure
CVVHD	Continuous veno-venous hemodialysis
CXR	Chest X-ray
D5W	5 % dextrose water
DAT	Direct antiglobulin test
DBP	Diastolic blood pressure
DC	Direct current
DCIS	Ductal carcinoma in situ
DDAVP	Desmopressin acetate
DEXA	Dual-energy X-ray absorptiometry
DFA	Direct fluorescent antibody
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone sulfate
DI	Diabetes insipidus
DIC	Disseminated intravascular coagulation
DIP	Distal interphalangeal joint
DKA	Diabetic ketoacidosis
DLBCL	Diffuse large B-cell lymphoma
DLCO	Diffusion capacity of lung for carbon monoxide
DM	Diabetes mellitus
DM1	Type 1 diabetes mellitus
DM2	Type 2 diabetes mellitus
DMARDs	Disease-modifying agents of rheumatoid disease
DNase	Deoxyribonuclease
DOT	Directly observed treatment
DPI	Dry powder inhaler
DPT	Diphtheria, pertussis, tetanus
dsDNA	Double-stranded DNA
DT	Delirium tremens
DVT	Deep vein thrombosis
Dx	Disease
EBV	Epstein–Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEG	Electroencephalography
EF	Ejection fraction
EGFR	Epidermal growth factor receptor
EHEC	Enterohemorrhagic *Escherichia coli*
EIEC	Enteroinvasive *Escherichia coli*
EMG	Electromyography
ENA	Extractable nuclear antigen
EPO	Erythropoietin
ER	Estrogen receptor, emergency room
ERCP	Endoscopic retrograde cholangiopancreatography
ESAS	Edmonton symptom assessment scale
ESBL	Extended spectrum β-lactamase
ESR	Erythrocyte sedimentation rate
ESRD	End-stage renal disease
ET	Essential thrombocytosis
ETEC	Enteropathogenic *Escherichia coli*
ETT	Endotracheal tube
EUS	Endoscopic ultrasound
FAP	Familial adenomatous polyposis
Fe	Iron
FEV1	Forced expiratory volume (1 s)
FFP	Fresh frozen plasma
FH	Family history
FHF	Fulminant hepatic failure
FiO_2	Fraction of inspired oxygen
FISH	Fluorescence in situ hybridization
FL	Follicular lymphoma
FMC	First medical contact
FNA	Fine needle aspirate
FNH	Focal nodular hyperplasia
FOB	Fecal occult blood
FRC	Functional residual capacity
FSGS	Focal segmental glomerulosclerosis
FSH	Follicle-stimulating hormone
FTA-ABS	Fluorescent treponemal antibody-absorption
FUO	Fever of unknown origin
FVC	Forced vital capacity
G6PD	Glucose-6-phosphate dehydrogenase deficiency
GBM	Glomerular basement membrane, glioblastoma multiforme
GBS	Guillain–Barre syndrome
GCS	Glasglow coma scale
GCSF	Granulocyte colony-stimulating factor
GERD	Gastroesophageal reflux disease
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transpeptidase
GI	Gastrointestinal
Gm	Gram stain
GN	Glomerulonephritis
GPA	Granulomatosis with polyangiitis
GU	Genitourinary

GVHD	Graft vs. host disease
GYN	Gynecological
H&N	Head and neck
Hb	Hemoglobin
HBV	Hepatitis B virus
HCL	Hairy cell leukemia
HCO_3	Bicarbonate
Hct	Hematocrit
HCV	Hepatitis C virus
HD	Hemodialysis
HDL	High density lipoprotein
HELLP	Hemolysis, elevated liver enzymes, low platelet count
HF	Heart failure
HHV8	Human herpes virus 8
HITT	Heparin-induced thrombocytopenia with associated thrombosis
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMG-CoA	3-Hydroxy-3-methylglutaryl coenzyme A
HNPCC	Hereditary non-polyposis colorectal cancer
HPV	Human papillomavirus
HR	Heart rate
hsCRP	High sensitivity C-reactive protein
HSIL	High-grade squamous intraepithelial lesion
HSP	Henoch–Schonlein purpura
HSV	Herpes simplex virus
HTLV	Human T-cell lymphoma virus
HU	Hounsfield unit
HUS	Hemolytic uremic syndrome
IADL	Instrumental activities of daily living
IBD	Inflammatory bowel disease
IBM	Inclusion body myositis
IBS	Irritable bowel syndrome
IBW	Ideal body weight
ICD	Implantable cardioverter-defibrillators
ICH	Intracerebral hemorrhage
ICP	Intracranial pressure
ICS	Inhaled corticosteroid
ICU	Intensive care unit
IDU	Injection drug use
IE	Infective endocarditis
IGRA	Interferon-gamma release assay
IL	Interleukin
INF	Interferon
INH	Inhaler
INO	Internuclear ophthalmoplegia
INR	International normalized ratio
IPF	Idiopathic pulmonary fibrosis
IPI	International prognostic index
IR	Immediate release
ITP	Idiopathic thrombocytopenic purpura
IV	Intravenous
IVC	Inferior vena cava
IVP	Intravenous pyelogram
JVP	Jugular venous pressure
KOH	Potassium hydroxide
KPS	Karnofsky performance status
KUB	Kidney, ureter, and bladder X-ray study
LAA	Left atrial abnormality
LABA	Long acting beta agonist
LAD	Left anterior descending
LAE	Left atrial enlargement
LAHB	Left anterior hemiblock
LAP	Leukocyte alkaline phosphatase
LBBB	Left bundle branch block
LCIS	Lobular carcinoma in situ
LCX	Left circumflex artery
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LES	Lambert–Eaton syndrome, lower esophageal sphincter
LFT	Liver function test
LH	Luteinizing hormone
Li	Lithium
LLL	Left lower lobe
LLQ	Left lower quadrant
LLSB	Left lower sternal border
LML	Left middle lobe
LMN	Lower motor neuron
LMWH	Low molecular weight heparin
LN	Lymph node
LOC	Level of consciousness
LP	Lumbar puncture
Lp(a)	Lipoprotein a
LPHB	Left posterior hemiblock
LPL	Lipoprotein lipase
LR–	Negative likelihood ratio
LR+	Positive likelihood ratio
LSD	Lysergic acid diethylamide
LSIL	Low-grade squamous intraepithelial lesion
LTBI	Latent tuberculosis infection
LUL	Left upper lobe
LUQ	Left upper quadrant
LUSB	Left upper sternal border
LV	Left ventricular
LVEDD	Left ventricular end diastolic diameter
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end systolic diameter
LVH	Left ventricular hypertrophy
LVOT	Left ventricular outflow tract
MAC	*Mycobacterium avium* complex
MAHA	Microangiopathic hemolytic anemia
MALT	Mucosa-associated lymphoid tissue
MAO	Monoamine oxidase
MAP	Mean arterial pressure
MCA	Middle cerebral artery
MCD	Minimal change disease
MCL	Mantle cell lymphoma
MCP	Metacarpal joint
MCTD	Mixed connective tissue disease
MCV	Mean corpuscular volume
MDI	Metered dose inhaler
MDS	Myelodysplastic syndrome
MEDD	Morphine equivalent daily dose
MELD	Model for end-stage liver disease
MEN	Multiple endocrine neoplasia
MEP	Maximal expiratory pressure
MF	Myelofibrosis, mycosis fungoides
Mg	Magnesium

MG	Myasthenia gravis
MGN	Membranous glomerulopathy
MGUS	Monoclonal gammopathy of uncertain significance
MHA-TP	Microhemagglutination assay for antibody to *Treponema pallidum*
MI	Myocardial infarction
MIBG	Iodine-131-meta-iodobenzylguanidine
MIBI	Methoxyisobutyl isonitrile
MIP	Maximal inspiratory pressure
MM	Multiple myeloma
MMI	Methimazole
MMR	Measles, mumps, and rubella
MMSE	Mini-mental state examination
MoCA	Montreal Cognitive Assessment
MPA	Microscopic polyangiitis
MPGN	Membranoproliferative glomerulopathy
MPO	Myeloperoxidase
MPS	Myeloproliferative syndrome
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant *Staphylococcus aureus*
MS	Mitral stenosis, multiple sclerosis
MSI	Microsatellite instability
MSK	Musculoskeletal
MSM	Men who have sex with men
MSSA	Methicillin-sensitive *Staphylococcus aureus*
MTC	Medullary thyroid cancer
MTP	Metatarsophalangeal joint
MVA	Mitral valve area, motor vehicle accident
MZL	Marginal zone lymphoma
N&V	Nausea and vomiting
Na	Sodium
NAAT	Nucleic acid amplification test
NCS	Nerve conduction studies
NCSE	Non-convulsive status epilepticus
NE	Norepinephrine
NEB	Nebulizer
NG	Nasogastric
NMDA	*N*-methyl-D-aspartic acid
NMS	Neuroleptic malignant syndrome
NNT	Number needed to treat
NPH	Normal pressure hydrocephalus, insulin
NPO	Nothing by mouth
NPV	Negative predictive value
NS	Normal saline
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
NSIP	Nonspecific interstitial pneumonia
NSTE	Non-ST elevation
NYD	Not yet diagnosed
NYHA	New York Heart Association
O&P	Ovum and parasites
OHS	Obesity hypoventilation syndrome
OHS	Obesity hypoventilation syndrome
OR	Odds ratio
OSA	Obstructive sleep apnea
Osmo	Osmolality
PA	Posterior–anterior
PAC	Paroxysmal atrial contraction
P_aCO_2	Arterial carbon dioxide pressure
PAN	Polyarteritis nodosa
P_aO_2	Arterial oxygen pressure
PAOP	Pulmonary artery occlusion pressure
PaP	Palliative prognostic score
PAP	Pulmonary artery pressure
PBC	Primary biliary sclerosis
PCOS	Polycystic ovarian syndrome
PCR	Polymerase chain reaction
PCWP	Pulmonary capillary wedge pressure
PDA	Patent ductus arteriosus, posterior descending artery
PE	Pulmonary embolism
PEA	Pulseless electrical activity
PEEP	Positive end expiratory pressure
PEF	Peak expiratory flow
PET	Positron emission tomography
PFO	Patent foramen ovale
PFT	Pulmonary function test
PIP	Proximal interphalageal joint
PJP	*Pneumocystis jirovecii* pneumonia
PML	Progressive multifocal leukoencephalopathy
PMN	Polymorphonuclear neutrophil
PMR	Polymyalgia rheumatica
PND	Paroxysmal nocturnal dyspnea
PNH	Paroxysmal nocturnal hemoglobinuria
PO	Oral
POEMS	Polyneuropathy, organomegaly, endocrinopathy, edema, M-protein, and skin abnormalities syndrome
PPS	Palliative performance scale
PPV	Positive predictive value
PR	Progesterone receptor, partial remission
PR3	Anti-proteinase-3
PRES	Posterior reversible leukoencephalopathy syndrome
PRN	As needed
PRV	Polycythemia ruba vera
PSA	Prostate-specific antigen
PSC	Primary sclerosing cholangitis
PSI	Pneumonia severity of illness score
PSV	Pressure support ventilation
PTCA	Percutaneous transluminal coronary angioplasty
PTCL	Peripheral T-cell lymphoma
PTH	Parathyroid hormone
PTLD	Post-transplant lymphoproliferative disease
PTP	Post transfusion purpura
PTT	Partial thromboplastin time
PTU	Propylthiouracil
PUD	Peptic ulcer disease
PVC	Paroxysmal ventricular contraction
PVD	Peripheral vascular disease
QID	Four times per day
RA	Rheumatoid arthritis
RAA	Right atrial abnormality
RAE	Right atrial enlargement
RAS	Renal artery stenosis
RBBB	Right bundle branch block
RBC	Red blood cell

RCA	Right coronary artery
RDW	Red blood cell distribution width
RF	Rheumatoid factor
RFS	Relapse free survival
RLL	Right lower lobe
RLQ	Right lower quadrant
RMR	Resting metabolic rate
RMSF	Rocky Mountain Spotted Fever
RNP	Ribonucleoprotein
RPGN	Rapidly progressive glomerulonephritis
RPR	Rapid plasma reagin
RR	Respiratory rate, relative risk
RRR	Relative risk reduction
RSBI	Rapid shallow breathing index
RSV	Respiratory syncytial virus
RSVP	Right ventricular systolic pressure
RTA	Renal tubular acidosis
RT-PCR	Reverse transcriptase polymerase chain reaction
RUL	Right upper lobe
RUQ	Right upper quadrant
RUSB	Right upper sternal border
SABA	Short acting beta agonist
SAH	Subarachnoid hemorrhage
SBP	Systolic blood pressure, spontaneous bacterial peritonitis
SCC	Squamous cell carcinoma
SCLC	Small cell lung cancer
SCT	Stem cell transplant
Sens	Sensitivity
SIADH	Syndrome of inappropriate antidiuretic hormone
SIRS	Systemic inflammatory response syndrome
SJS	Stevens-Johnson syndrome
SK	Streptokinase
SLE	Systemic lupus erythematosus
SLL	Chronic lymphocytic lymphoma
SNRI	Serotonin-norepinephrine reuptake inhibitor
Spc	Specificity
SPN	Solitary pulmonary nodule
SR	Slow release
SSc	Systemic sclerosis
SSEP	Somatosensory evoked potentials
SSRI	Selective serotonin reuptake inhibitor
SSS	Sick sinus syndrome
SSSS	Staphylococcal scalded skin syndrome
STE	ST elevation
SV	Stroke volume
SVC	Superior vena cava
SVR	Systemic vascular resistance
SVT	Supraventricular tachycardia
TB	Tuberculosis
TBI	Total body irradiation
TCA	Tricyclic antidepressants
TD	Transdermal
TEE	Transesophageal echocardiogram
TEN	Toxic epidermal necrolysis
TGL	Triglyceride
TIA	Transient ischemic attack
TIBC	Total iron-binding capacity
TID	Three times per day
TIMI	Thrombolysis in myocardial infarction
TIPS	Transjugular intrahepatic portosystemic shunt
TLC	Total lung capacity
TMP/SMX	Trimethoprim-sulfamethoxazole
TNF	Tumor necrosis factor
TP-EIA	*Treponema pallidum* enzyme immunoassay
TPN	Total parenteral nutrition
TPO	Thyroid peroxidase
TPPA	*Treponema pallidum* particle agglutination assay
TRH	Thyrotropin releasing hormone
TSH	Thyroid stimulating hormone
TST	Tuberculin skin test
TTE	Transthoracic echocardiogram
TTP	Thrombotic thrombocytopenic purpura
TUR	Transurethral resection
TURP	Transurethral resection of prostate
U/A	Urinalysis
UGI	Upper gastrointestinal
UIP	Usual interstitial pneumonia
UMN	Upper motor neuron
UNC	Urine net charge
US	Ultrasound
UTI	Urinary tract infection
UV	Ultraviolet
V/Q	Ventilation/perfusion
VAP	Ventilator-associated pneumonia
VC	Vital capacity
VDRL	Venereal Disease Research Laboratory
VF	Ventricular fibrillation
VHL	Von Hippel–Lindau syndrome
VLDL	Very low density lipoprotein
VRE	Vancomycin-resistant enterococci
VSD	Ventricular septal defect
VT	Ventricular tachycardia
vWD	Von Willebrand disease
VZV	Varicella zoster virus
WBC	White blood cell
WPW	Wolff–Parkinson–White

Appendix C
COMMON LABORATORY VALUES AND UNIT CONVERSION

Note: normal ranges are provided for general reference only. The normal values for individual institution may vary significantly due to assay used and population tested. An excellent resource is the *AMA Manual of Style: A Guide for Authors and Editors.* 10th ed. New York, NY: Oxford University Press; 2007

BLOOD COUNTS

	SI units	US units	SI → US ratio	US → SI ratio
Hematocrit				
Male	0.41–0.50	41–50 %	100	0.01
Female	0.35–0.45	35–45 %	100	0.01
Hemoglobin				
Male	140–175 g/L	14–17.5 g/dL	0.1	10
Female	120–160 g/L	12–16 g/dL	0.1	10
RBC count				
Male	$4.5–5.9 \times 10^{12}$/L	$4.5–5.9 \times 10^{6}$/μL	1	1
Female	$4.0–5.2 \times 10^{12}$/L	$4.0–5.2 \times 10^{6}$/μL	1	1
Platelet count	$150–440 \times 10^{9}$/L	$150–440 \times 10^{3}$/μL	1	1
WBC count	$4.5–11.0 \times 10^{9}$/L	$4.5–11.0 \times 10^{3}$/μL	1	1
Neutrophil	$1.7–7.3 \times 10^{9}$/L	$1.7–7.3 \times 10^{3}$/μL	1	1
Lymphocyte	$1.0–4.8 \times 10^{9}$/L	$1.0–4.8 \times 10^{3}$/μL	1	1
Monocyte	$0.08–0.70 \times 10^{9}$/L	$0.08–0.70 \times 10^{3}$/μL	1	1
Eosinophil	$0.04–0.40 \times 10^{9}$/L	$0.04–0.40 \times 10^{3}$/μL	1	1
Basophil	$0–0.10 \times 10^{9}$/L	$0–0.10 \times 10^{3}$/μL	1	1
CD4 count	$0.64–1.18 \times 10^{9}$/L	640–1175/mm^3	1000	0.001
CD8 count	$0.34–0.88 \times 10^{9}$/L	335–875/mm^3	1000	0.001
CD4:CD8 ratio	1.0–4.0	1.0–4.0	1	1
Reticulocyte count	0.005–0.025	0.5–2.5 %	100	0.01

COAGULATION STUDIES

	SI units	US units	SI → US ratio	US → SI ratio
aPTT	22.1–35.1 s	22.1–35.1 s	1	1
Bleeding time	2–9.5 min	2–9.5 min	1	1
D-dimer (adjust for age)	<0.5 mg/L	<0.5 μg/mL	1	1
INR	0.8–1.2	0.8–1.2	1	1
PT	10–13 s	10–13 s	1	1
Thrombin time	16–24 s	16–24 s	1	1

TUMOR MARKERS

	SI units	US units	SI → US ratio	US → SI ratio
AFP	<15 pμg/L	<15 ng/mL	1	1
β2-microglobulin	0–2 mg/L	0–2 μg/mL	1	1
CA 19–9	<37 kU/L	<37 U/mL	1	1
CA 27.29	<32 kU/L	<32 U/mL	1	1
CA 125	<35 kU/L	<35 U/mL	1	1

TUMOR MARKERS (CONT'D)	SI units	US units	SI → US ratio	US → SI ratio
CEA	<4 µg/L	<4 ng/mL	1	1
HCG	<5 IU/L	<5 mIU/mL	1	1
PSA	<4 µg/L	<4 ng/mL	1	1
Serum protein electrophoresis				
Total protein	60–80 g/L	6–8 g/dL	0.1	10
Albumin	33–48 g/L	3.3–4.8 g/dL	0.1	10
Alpha1 globulin	2–4 g/L	0.2–0.4 g/dL	0.1	10
Alpha2 globulin	5–10 g/L	0.5–1.0 g/dL	0.1	10
Beta globulin	6–11 g/L	0.6–1.1 g/dL	0.1	10
Gamma globulin	7–17 g/L	0.7–1.7 g/dL	0.1	10

CHEMISTRY	SI units	US units	SI → US ratio	US → SI ratio
Albumin	35–50 g/L	3.5–5 g/dL	0.1	10
Calcium				
Regular	2.05–2.55 mmol/L	8.2–10.2 mg/dL	4	0.25
Ionized	1.1–1.4 mmol/L	4.5–5.6 mg/dL	4	0.25
Cardiac enzymes				
CK	40–150 U/L	40–150 U/L	1	1
Troponin				
Troponin I	0–0.1 µg/L	0.1 ng/mL	1	1
Troponin T	0–0.03 µg/L	0.03 ng/mL	1	1
CRP (high sens)	<8 mg/L	<8 mg/L	1	1
Electrolytes panel				
Na	136–142 mmol/L	136–142 mEq/L	1	1
K	3.5–5.0 mmol/L	3.5–5.0 mEq/L	1	1
Cl	96–106 mmol/L	96–106 mEq/L	1	1
HCO_3	22–30 mmol/L	22–30 mEq/L	1	1
Urea (BUN)	2.9–7.1 mmol/L	8–20 mg/dL	2.76	0.36
Creatinine	50–120 µmol/L	0.6–1.2 mg/dL	0.011	88.4
Cr clearance	1.20–2.30 mL/s	75–125 mL/min	59.9	0.017
Glucose				
Fasting	4.2–6.4 mmol/L	75–115 mg/dL	18.02	0.0555
Postprandial 2 h	<6.7 mmol/L	<120 mg/dL	18.02	0.0555
ESR				
Male	0–17 mm/h	0–17 mm/h	1	1
Female	1–25 mm/h	1–25 mm/h	1	1
Folate	7.0–39.7 nmol/L	3.1–17.5 ng/mL	0.44	2.27
Iron studies				
Ferritin				
Male	30–300 µg/L	30–300 ng/mL	1	1
Female	100–200 µg/L	100–200 ng/mL	1	1
Iron	5.4–28.7 µmol/L	30–160 µg/dL	5.56	0.18
TIBC	40.8–76.7 µmol/L	228–428 µg/dL	5.56	0.18
Transferrin	0–0.4 µg/L	0–0.4 ng/mL	1	1
Lipid profile				
LDL	<3.36 mmol/L	<130 mg/dL	38.5	0.026
HDL	>1.04 mmol/L	>40 mg/dL	38.5	0.026
Total cholesterol	<5.15 mmol/L	<200 mg/dL	38.5	0.026
Triglycerides	<1.8 mmol/L	<160 mg/dL	90.9	0.011

CHEMISTRY (CONT'D)				
	SI units	**US units**	**SI → US ratio**	**US → SI ratio**
Liver function tests				
AST	20–48 U/L	20–48 U/L	1	1
ALT	10–40 U/L	10–40 U/L	1	1
ALP	50–120 U/L	50–120 U/L	1	1
Bilirubin				
Total	5–21 µmol/L	0.3–1.2 mg/dL	0.058	17.1
Direct	<3.4 µmol/L	<0.2 mg/dL	0.058	17.1
LDH	50–200 U/L	50–200 U/L	1	1
Magnesium	0.8–1.2 mmol/L	1.8–3.0 mg/dL	2.4	0.41
Phosphate	0.97–1.45 mmol/L	3.0–4.5 mg/dL	3.1	0.32
Uric acid	240–510 µmol/L	4.0–8.5 mg/dL	0.017	60
Vitamin B12				
Normal	>185 pmol/L	>250 pg/mL	1.35	0.74
Deficient	<92 pmol/L	<125 pg/mL	1.35	0.74
Amylase	25–100 U/L	25–100 U/L	1	1
Lipase	0–160 U/L	0–160 U/L	1	1

ENDOCRINE TESTING				
	SI units	**US units**	**SI → US ratio**	**US → SI ratio**
ACTH	<11.5 pmol/L	<52 pg/mL	4.52	0.22
Calcitonin				
Male	<2.3 pmol/L	<8 pg/mL	3.42	0.292
Female	<4.7 pmol/L	<16 pg/mL	3.42	0.292
Cortisol				
8 am–noon	138–690 nmol/L	5–25 µg/dL	0.036	27.6
Noon–8 pm	138–414 nmol/L	5–15 µg/dL	0.036	27.6
8 pm–8 am	0–276 nmol/L	0–10 µg/dL	0.036	27.6
EPO	5–18.5 IU/L	5–18.5 mIU/mL	1	1
Glucagon	20–100 ng/L	20–100 pg/mL	1	1
Insulin	14–140 pmol/L	2–20 µU/mL	0.14	6.95
Metanephrine				
Plasma	<0.5 nmol/L	<0.5 nmol/L	1	1
Urine, 24 h	<5 µmol	<1 mg	0.20	5.1
Norepinephrine	89–473 nmol	15–80 µg	0.17	5.9
Urine, 24 h				
Prolactin				
Male	0–20 µg/L	0–20 ng/mL	1	1
Female	0–15 µg/L	0–15 ng/mL	1	1
PTH	10–60 ng/L	10–60 pg/mL	1	1
Testosterone				
Men	9.4–37.1 nmol/L	270–1070 ng/dL	28.6	0.035
Women	0.21–2.98 nmol/L	6–86 ng/dL	28.6	0.035
Thyroglobulin	0–60 µg/L	0–60 ng/mL	1	1
TSH	0.5–5.0 mU/L	0.5–5.0 µU/mL	1	1
T3				
Free	3.5–6.5 pmol/L	230–420 pg/dL	65	0.015
Total	0.92–2.78 nmol/L	60–181 ng/dL	65	0.015
T4				
Free	10.3–35 pmol/L	0.8–2.7 ng/dL	0.078	13
Total	58–140 nmol/L	4.5–10.9 µg/dL	0.078	13

ENDOCRINE TESTING (CONT'D)

	SI units	US units	SI → US ratio	US → SI ratio
Vitamin D				
1,25–$(OH)_2$–vit D	60–108 pmol/L	25–45 pg/mL	0.42	2.4
25–(OH) vit D	35–150 nmol/L	14–60 ng/mL	0.4	2.5

DRUG LEVELS

	SI units	US units	SI → US ratio	US → SI ratio
Acetaminophen				
Therapeutic range	66–199 µmol/L	10–30 µg/mL	0.15	6.6
Toxic range	>1324 µmol/L	>200 µg/mL	0.15	6.6
Amitriptyline				
Therapeutic range	433–903 nmol/L	120–250 ng/mL	0.28	3.6
Toxic range	>1805 nmol/L	>500 ng/mL	0.28	3.6
Carbamazepine				
Therapeutic range	26–51 µmol/L	6–12 µg/mL	0.24	4.2
Toxic range	>63 µmol/L	>15 µg/mL	0.24	4.2
Clonazepam				
Therapeutic range	48–190 nmol/L	15–60 ng/mL	0.31	3.2
Toxic range	>254 nmol/L	>80 ng/mL	0.31	3.2
Clozapine				
Therapeutic range	0.6–1.0 µmol/L	200–350 ng/mL	333	0.003
Cocaine				
Toxic dose	>3300 nmol/L	>1000 ng/mL	0.30	3.3
Diazepam				
Therapeutic range	0.35–3.51 µmol/L	100–1000 ng/mL	285	0.0035
Toxic range	>17.55 µmol/L	>5000 ng/mL	285	0.0035
Digoxin				
Therapeutic range	1.0–2.6 nmol/L	0.8–2.0 ng/mL	0.78	1.28
Toxic range	>3.2 nmol/L	>2.5 ng/mL	0.78	1.28
Ethanol				
Toxic dose	>65 mmol/L	>300 mg/dL	4.6	0.22
Gentamicin				
Peak	16.7–20.9 µmol/L	8–10 µg/mL	0.48	2.1
Trough	<4.2–8.4 µmol/L	<2–4 µg/mL	0.48	2.1
Imipramine				
Therapeutic range	446–893 nmol/L	125–250 ng/mL	0.28	3.57
Toxic range	>1784 nmol/L	>500 ng/mL	0.28	3.57
Lidocaine				
Therapeutic	6.4–26 µmol/L	1.5–6.0 µg/mL	0.23	4.3
Lithium				
Therapeutic	0.6–1.2 nmol/L	0.6–1.2 mEq/L	1	1
Toxic range	>2 mmol/L	>2 mEq/L	1	1
Methadone				
Therapeutic range	0.32–1.29 µmol/L	100–400 ng/mL	313	0.0032
Toxic range	>6.46 µmol/L	>2000 ng/mL	313	0.0032
Morphine				
Therapeutic range	35–280 nmol/L	10–80 ng/mL	0.29	3.5
Toxic range	>700 nmol/L	>200 ng/mL	0.29	3.5
Nortriptyline				
Therapeutic range	0.19–0.65 nmol/L	50–170 ng/mL	263	0.0038
Toxic range	>1.9 µmol/L	>500 ng/mL	263	0.0038

DRUG LEVELS (CONT'D)	SI units	US units	SI → US ratio	US → SI ratio
Phenytoin				
Therapeutic range	40–79 µmol/L	10–20 µg/mL	0.25	3.95
Toxic range	>79 µmol/L	>20 µg/mL	0.25	3.95
Salicylates				
Therapeutic range	1086–2172 µmol/L	150–300 µg/mL	0.14	7.24
Toxic range	>2172 µmol/L	>300 µg/mL	0.14	7.24
Theophylline				
Therapeutic range	44–111 µmol/L	8–20 µg/mL	0.18	5.5
Toxic range	>110 µmol/L	>20 µg/mL	0.18	5.5
Tobramycin				
Peak	17–21 µmol/L	8–10 µg/mL	0.44	2.25
Trough	<9 µmol/L	<4 µg/mL	0.44	2.25
Valproic acid				
Therapeutic range	347–1040 µmol/L	50–150 µg/mL	0.14	6.9
Toxic range	>1040 µmol/L	>150 µg/mL	0.14	6.9
Vancomycin				
Peak	12–18 µmol/L	18–26 µg/mL	1.67	0.6
Trough	3–7 µmol/L	5–10 µg/mL	1.67	0.6
Amikacin				
Peak	43–60 µmol/L	25–35 µg/mL	0.59	1.7
Trough	6.8–13.7 µmol/L	4–8 µg/mL	0.59	1.7

Appendix D
HISTORY TEMPLATE

BASIC SCHEME

CHIEF COMPLAINT:

HISTORY OF PRESENT ILLNESS:
Onset
Position/posture
Previous history
Progression
Quality
Radiating
Severity
Temporal factors
Treatment
Understanding

Aggravating
Alleviating
Associated symptoms

Etiologies
Risk factors
Complications

How has illness affected your life
Support systems
Worries, fears
Expectations

PAST MEDICAL HISTORY:
Hospitalization (time, tx, recovery)
Medical illnesses (time, tx, recovery)
Injuries (time, tx, recovery)

MEDICATIONS:
drug name, dose, route, frequency

ALLERGIES:

IMMUNIZATIONS:

SOCIAL HISTORY:
☐ **Living arrangement, marital**
☐ **Support system** ☐ Hobbies

☐ **ADLs** ☐ **IADLs**
☐ Education ☐ **Occupation**

☐ **Smoking** ☐ **Alcohol**
☐ **Illicit drugs** ☐ Diet

FAMILY HISTORY:

Father	**Mother**
Siblings	Children
☐ **Cancer**	☐ **Heart disease**
☐ Diabetes	☐ Genetic disease

REVIEW OF SYSTEMS

CONSTITUTIONAL:
☐ **Weight Δ** ☐ **Energy**
☐ **Fever, chills** ☐ **Night sweats**
☐ Appetite Δ ☐ Sleep
☐ Mood Δ

HEAD AND NECK:
☐ **Vision Δ** ☐ **Diplopia Δ**
☐ Smell ☐ Rhinorrhea
☐ Sinusitis ☐ Epistaxis
☐ **Hearing Δ** ☐ Discharge
☐ Tinnitus ☐ Vertigo
☐ Sore throat ☐ Teeth
☐ Tongue ☐ Oral lesions
☐ **Neck pain** ☐ Neck mass

CARDIAC:
☐ **Chest pain** ☐ **Dyspnea**
☐ **Syncope** ☐ **Palpitations**
☐ **Orthopnea** ☐ **PND**
☐ **Claudication** ☐ **Leg edema**
☐ Murmurs ☐ Hypertension
☐ Rheumatic fever

RESPIRATORY:
☐ **Dyspnea** ☐ **Cough**
☐ **Sputum** ☐ **Hemoptysis**
☐ **Pleuritic chest pain**

GASTROINTESTINAL:
☐ **Dysphagia** ☐ Odynophagia
☐ **Heartburn** ☐ Reflux
☐ **N&V** ☐ **Hematemesis**
☐ **Melena** ☐ **Abd pain**
☐ **Diarrhea** ☐ **Constipation**
☐ **Bowel habits** ☐ **Hematochezia**
☐ Bloating ☐ Flatus
☐ Pale stool ☐ Jaundice
☐ Hemorrhoid

GENITOURINARY:
☐ **Dysuria** ☐ **Frequency**
☐ **Urgency** ☐ Hesitancy
☐ **Incontinence** ☐ Slow stream
☐ **Hematuria** ☐ Nocturia
☐ Discharge
☐ Libido ☐ **Impotence**

RHEUMATOLOGIC:
☐ **Joint pain, swelling, redness**
☐ **AM stiffness** ☐ **Back pain**
☐ Myalgia ☐ Arthralgia
☐ Skin rash ☐ Raynaud's
☐ Dry eyes ☐ Dry mouth
☐ Oral ulcers ☐ Hair loss
☐ Photosensitivity
☐ Psoriasis ☐ IBD

OBS/GYN:
☐ **Menarche age** ☐ LMP
☐ Cycle regular ☐ Period length
☐ Periods freq. ☐ Period volume
☐ **Menopause age** ☐ HRT
☐ **Abnormal bleeding**
☐ **No. of preg.** ☐ Difficult preg.
☐ **Contraception** ☐ STDs
☐ Vaginal dryness or discharge
☐ Dyspareunia

BREASTS:
☐ **Masses** ☐ Swelling
☐ **Nipple discharge**
☐ Pain
☐ Self breast exam

ENDOCRINE:
☐ **Polydipsia** ☐ Polyphagia
☐ **Polyuria** ☐ Galactorrhea
☐ **Heat or cold tolerance**

NEUROPSYCHIATRIC:
☐ **Unconscious** ☐ **Syncope**
☐ **Vertigo** ☐ Dizziness
☐ Memory loss ☐ Dysphasia
☐ Head trauma ☐ Strokes
☐ **Headaches** ☐ **Seizures**
☐ **Weakness** ☐ **Paresis**
☐ Clumsiness ☐ Balance/gait

☐ **Depression** ☐ Suicidal
☐ **Anxiety** ☐ Previous

SKIN:
☐ **Rashes** ☐ **Lumps**
☐ Pruritus ☐ Pigment Δ

REMARKS:

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Integrated Symptom-Based and Issue-Based Approach from *Approach to Internal Medicine*, 4th Edition

David Hui, Alexander A. Leung, Raj Padwal

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